

https://dspace.org/

Impact of dexmedetomidine on postoperative biomarkers, length of hospitalisation and mortality in patients undergoing coronary artery bypass graft surgery

Motshabi, Palesa Mamoseki Violet

2019

https://hdl.handle.net/10539/29859

Motshabi, Palesa Mamoseki Violet, Impact of dexmedetomidine on postoperative biomarkers, length of hospitalization and mortality in patients undergoing coronary artery bypass graft surgery, University of the Witwatersrand, Johannesburg, <http://hdl.handle.net/10539/29859>

Downloaded from a DSpace repository. https://dspace.org/

IMPACT OF DEXMEDETOMIDINE ON POSTOPERATIVE BIOMARKERS, LENGTH OF HOSPITALISATION AND MORTALITY IN PATIENTS UNDERGOING CORONARY ARTERY BYPASS GRAFT SURGERY

Palesa Mamoseki Violet Motshabi

A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfilment of the requirements for the degree of Doctor of Philosophy.

Johannesburg 2019

DEDICATION

This thesis is dedicated to:
The late Papa, Modise Ambrose Motshabi (29 March 1929 – 29 October 2006) for always believing in me
My mother, Khukhu Mabel Motshabi, for instilling the principles of hard work and strength of character that make me the woman I am today
My sister, Tsienyane Precious Motshabi and her children, for supporting and caring for my mother while I studied
My helper, Dipuo Majela, for caring for my children as if they were her own
My assistant Dineo Tlale for doing all my administrative work
My adorable daughters, Mpho Matswai Chakane and Mosa Mmutsi Chakane, for unconditionally loving Mommy and for inspiring me to be the best that I can be
My loving, supportive, inspirational, protective and encouraging husband, Moretsele Morisson Chakane, for being the driving force behind achieving the dream.

DECLARATION

I, Palesa Mamoseki Violet Motshabi, declare that this thesis is my own work. It is submitted for the degree of Doctor of Philosophy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

Palesa Mamoseki Violet Motshabi

Johannesburg, 2019

PRESENTATIONS AND PUBLICATIONS ARISING FROM THIS STUDY

Oral presentations

1. Johannesburg Perioperative Cardiothoracic Congress, 2016
    - Dexmedetomidine in coronary artery bypass graft surgery: is it cardioprotective?
    - Ethnicity and coronary artery bypass graft surgery
2. South African Society of Anaesthesia Congress, February 2017
    - Dexmedetomidine in cardiac surgery: the real facts
3. The Department of Anaesthesiology, University of Witwatersrand, April 2017
    - The predictive value of hs-cTnT, NT-proBNP and CRP towards short-term outcomes during CABG surgery
4. The Department of Anaesthesiology, University of Witwatersrand, June 2017
    - Part II refresher course – Biomarkers in cardiac disease

Journal publications

1. Motshabi P. Myocardial ischemia during coronary artery bypass graft surgery: a review of the pathophysiology (Part 1). South African Journal of Anaesthesia and Analgesia. 2012;18(2):70–74.
2. Motshabi P. Myocardial ischemia during coronary artery bypass graft surgery: a review of intervention strategies (Part 2). South African Journal of Anaesthesia and Analgesia. 2012;18(3):134–138

ABSTRACT

Background

Coronary artery bypass graft surgery, a surgical procedure performed to alleviate the symptoms of ischaemic heart disease and improve prognosis on cardiopulmonary bypass, is beneficial in patients with ischaemic heart disease, however it is not without deleterious adverse clinical events and mortality due to its associated inflammatory and stress response. Dexmedetomidine, an α–2 adrenergic agonist, is a promising drug with a potential towards myocardial protection due to its favourable pharmacological profile. This study investigated the impact of dexmedetomidine compared to placebo on high sensitivity troponin in patients undergoing coronary artery bypass graft surgery on cardiopulmonary artery bypass in a randomised controlled trial. Secondary endpoints included mortality and the length of hospitalization. Subsequently, a systematic review and meta-analysis of randomised controlled trials on the effects of dexmedetomidine on conventional troponin (cTn) compared to control was conducted.

Methods

A randomised, controlled, double-blind trial was undertaken to investigate the effects of dexmedetomidine on myocardial ischaemia and short-term outcomes. A total of 90 patients admitted to the Charlotte Maxeke Johannesburg Academic hospital in Johannesburg for coronary artery bypass graft surgery were enrolled to receive either dexmedetomidine 0.3–0.7 μg/kg/hr or placebo. Sample size estimation was calculated on studies reporting the effects on cTn, due to paucity of data on hs-cTnT, and 45 received dexmedetomidine, 45 received placebo. The primary endpoint was the effect of dexmedetomidine on 24-hour postoperative levels of high-sensitivity cardiac troponin T (hs-cTnT). Blood was collected at baseline and 24-hours postoperatively for hs-cTnT testing, length of stay and 30-day mortality data was recorded. For the systematic review, a database search of PubMed Central, Cochrane Library, Web of Science and Scopus was conducted for the period between January 2008 and April 2018. A total of 82 studies was screened, and 14 studies with 1434 patients were included in the final analysis.

Results

Clinical and laboratory data were available for all 90 patients enrolled on the clinical trial. The change (delta) in hs-cTnT levels from baseline to 24 hours postoperatively was not statistically different between the dexmedetomidine [353.5(231.5–621.5) ng/L] and

placebo [301(217–648) ng/L] groups, p = 0.59. Mortality rates were 5(11%) in the intervention group and 4(9%) in the placebo group. The probability of mortality at 30-days and in 1-year was not different (RRR 3; 95% CI 0.3, 27.76; p = 0.1263) and (RRR 1.25; 95% CI 0.36, 4.35; p = 0.38) between groups. Length of stay in intensive care was not statistically different [3(2–4) vs. 3(2–4) days, p = 0.33]. Patients who received dexmedetomidine had a significantly longer stay in hospital compared with the placebo group, 11.2(8.4) vs. 8.3(3.7) days, p = 0.044. A statistically significant correlation with length of hospitalisation was found, (r = 0.2164, p = 0.0417), and in a simultaneous quantile regression analysis the association with hospital stay in the first 7 days was statistically significant (coefficient 0.8, SE 0.31, t 2.58, 95% CI 0.18–1.40, p = 0.012). A post hoc power analysis showed that the study was underpowered for evaluating the effects on hs-cTnT. The systematic review revealed that dexmedetomidine use in general cardiac surgery statistically significantly reduced estimates of cTn, TNFα and IL-6 levels at 24-hours/day-1 post-surgery compared to control (MD -0.35; 95% CI -0.44, -0.25; p<0.00001, I^2 = 94%), (SMD -2.37; 95% CI -3.60, -1.15; p<0.001, I^2=76%) and (SMD -1.26; 95% CI -1.97, -0.55; p=0.0005, I^2=42%) dexmedetomidine and controls, respectively. There was, however, significant heterogeneity in cTn and TNFα estimates. A significant difference in the coronary artery bypass graft sub-group analysis in cTn and creatinine kinase muscle and brain (CKMB) changes at 24-hours/day-1 in the dexmedetomidine group was not found.

Conclusion

Results from the randomised controlled clinical trial proved inconclusive. Although dexmedetomidine did not attenuate the rise in hs-cTnT levels 24-hours postoperatively when compared with placebo, the post hoc power analysis showed that the study was underpowered to make generalised conclusions. Thus, data from clinical trials from cTn cannot be extrapolated to hs-cTnT. A meta-analysis of the existing literature in cTn provides a promising signal and highlights further avenues to explore in larger clinical trials in this area.

ACKNOWLEDGEMENTS

I would like to acknowledge the University of Witwatersrand community, the Faculty of Health Sciences and the School of Clinical Medicine for the various resources that contributed to this study.

The following departments and individuals are acknowledged for their valued contributions:

- The former vice chancellor and principal of the University of Witwatersrand, Professor Loyiso Nongxa, for the start-up funding from the Vice Chancellor's Fund in 2012
- The South African Medical Research Council, for the Research Fellowship Grant awarded in 2016
- University of Witwatersrand's Faculty of Health Sciences, for the top-up research grant in 2016
- The department of Cardiology at Chris Hani Baragwanath Academic Hospital and the department of Haematology at Charlotte Maxeke Johannesburg Academic Hospital, for lending me fridge space for specimen storage
- Smith Medical, for placing infusion pumps in the unit for drug administration during the study
- Covidien, for placement of in-vivo optical spectroscopy and bi-spectral index monitors for use during the study
- Abbvie, for donating a batch of dexmedetomidine study drug samples
- Dr Teema Nankoo for setting up the randomisation and assisting with Medicines Control Council approval
- Mrs Karin Robertson, for assistance with randomisation, blinding during the trial and the daily running of the study
- Dr Atul Patel and the Department of Cardiothoracic Surgery, adult unit, for assisting with the enrolment of the study patients
- Dr Katherina Van De Donck for assisting with data collection
- Dr Ntombi Biyase for assisting with data capture and telephonic follow-up of patients
- The heads of Schools of Pathology and Clinical Medicine, professors Mahlangu and Lukhele for valuable advice, guidance and support
- The Department of Anaesthesiology for their support
- The cardiac anaesthesia team, who patiently participated in this study
- The anaesthesiology registrars who assisted with logistics during the study

- Professor Elena Libhaber, Michel Muteba, Victor Kanje and Lukhanyo Nyati for assistance with statistical analysis
- Professor John Pettifor and Dr Aceme Nyika for assistance with my write-up
- Dr Mark Allen for lessons on electronic formatting, editing and EndNote use
- Mr Bill Steele and Dr Kemp for assistance with editing
- Mr Clive Moodly, Ms Bongiwe Qakaza and the National Health Laboratory Services staff at Chris Hani Baragwanath and Charlotte Maxeke Johannesburg hospitals for logistic support and assistance with biochemical tests
- Mr Abie Tlhabanelo for being my unofficial, unpaid research assistant
- Dr Raquel Duarte from the Department of Internal Medicine at Charlotte Maxeke Johannesburg Academic Hospital for assisting with the running of ELISA tests for interleukins levels
- Dr Reitze Rodseth and Ms Kedibone Moagi for assistance with the systematic review
- Ms Tholakele Nkosi and the finance division at the Faculty of Health Sciences for assistance with accounts, insurance and suppliers' payments
- The patients who were kind enough to agree to participate in this clinical trial despite being gravely ill
- My friends, Palesa Mogane, Matlhodi Moloto and Matshosane Maiten, for their emotional support
- Professor. Andrew Levin for his advice in refining the conceptual framework of the study
- Professor. Michael Hasenkam for the research input and all the advice and support
- My mentor, Professor. Stanton Shernan of Harvard University, for making me believe I could do this
- My supervisors, Professor. Mashudu Nethononda and Professor. Christina Lundgren, for their patience, valuable guidance and support.

TABLE OF CONTENTS

DEDICATION II
DECLARATION III
ABSTRACT V
ACKNOWLEDGEMENTS VII
TABLE OF CONTENTS IX
TABLE OF FIGURES XV
LIST OF TABLES XVII
LIST OF ABBREVIATIONS XIX
CHAPTER 1: INTRODUCTION 1
1.1 Background and rationale of the study 1
1.2 The epidemiology of coronary artery disease 2
1.3 Inflammation and the stress response to surgery 4
1.4 Myocardial ischemia-reperfusion injury 5
1.5 Myocardial protection 6
1.6 Anaesthetic agents and cardiac protection 7
1.7 Pharmacoethnicity 8
1.8 Aims of the study 8
1.9 Objectives of the study 8
1.10 Project outline 8
1.10.1 Hypothesis 8
1.10.2 Demarcation of the study 9
1.10.3 Study population 9
1.10.4 Ethical considerations 9
1.10.5 Research methodology 10
1.10.5.1 Study design 10
1.10.5.2 Inclusion criteria 10
1.10.5.3 Exclusion criteria 10
1.10.5.4 Primary outcome 10
1.10.5.5 Secondary outcomes 10
1.10.6 Blood sample analysis 11
1.10.7 Statistical analysis, sample size and power estimates 11
1.10.7.1 Sample size and power estimates 11

1.10.7.2 Statistical analysis 11
1.11 Significance of the study 12
1.12 Potential limitations 12
1.13 Thesis outline 12
CHAPTER 2 DEXMEDETOMIDINE, BIOMARKERS AND CLINICAL OUTCOMES 14
2.1 Literature review 14
2.1.1 Background 14
2.1.2 Inflammatory markers in cardiac patients 14
2.1.3 Myocardial ischaemic markers 16
2.1.4 Myocardial protection during cardiac surgery 20
2.1.5 Anaesthetic agents and cardiac protection 23
2.1.6 Alpha-2 agonists and myocardial protection in cardiac surgery 25
2.1.7 Dexmedetomidine 26
2.1.8 Dexmedetomidine and myocardial protection 28
2.1.8.1 Dexmedetomidine and myocardial protection in animal studies 28
2.1.8.2 Dexmedetomidine and myocardial protection in vascular patients 30
2.1.8.3 Dexmedetomidine and catecholamines in CABG surgery 31
2.1.8.4 Dexmedetomidine and inflammatory markers in CABG surgery 32
2.1.8.5 Dexmedetomidine and ischaemic markers in CABG surgery 34
2.1.8.6 Dexmedetomidine, length of stay in hospital/ICU and mortality in CABG surgery 40
2.1.9 Summary of the literature regarding the impact of dexmedetomidine in CABG surgery 42
2.2 Dexmedetomidine, biomarkers and prediction of outcome 43
2.3 Ethnicity and CAD, dexmedetomidine and pharmacoethnicity 45
2.3.1 Ethnicity and CAD 45
2.3.2 Dexmedetomidine, pharmacoethnicity and cTn 47
CHAPTER 3 : RESEARCH METHODOLOGY 50
3.1 Hypothesis 50
3.2 Methods 50
3.2.1 Study design 50
3.2.2 Study population 51
3.2.3 Inclusion criteria 51
3.2.4 Exclusion criteria 51

3.3 Anaesthetic technique 52
3.4 Blood sample storage 56
3.5 Postoperative management 56
3.6 Blood sample analysis 56
3.7 Outcome measures 57
3.7.1 Primary outcome 57
3.7.2 Secondary outcomes 57
3.8 Statistical analysis, sample size and power estimates 58
CHAPTER 4 : DEXMEDETOMIDINE vs PLACEBO 61
4.1 Introduction 61
4.1.1 Baseline characteristics: dexmedetomidine vs placebo 61
4.1.2 Effects of dexmedetomidine on hs-cTnT 62
4.1.3 Effects of dexmedetomidine on interleukins 64
4.1.4 Effects of dexmedetomidine on length of stay in ICU 65
4.1.5 Effects of dexmedetomidine on hospital stay 65
4.1.6 Effects of dexmedetomidine on 30-day and 1-year mortality 66
4.1.7 Effects of dexmedetomidine on adverse events 66
4.2 Reliability of data 67
4.3 Discussion 68
4.3.1 Dexmedetomidine and ischaemic marker hs-cTnT 68
4.3.2 Dexmedetomidine and inflammatory markers 73
4.3.3 Dexmedetomidine and ICU stay 75
4.3.4 Dexmedetomidine and hospital stay 79
4.3.5 Dexmedetomidine and mortality 81
4.3.6 Dexmedetomidine and adverse outcomes 82
4.4 Conclusions and recommendations 83
4.5 Limitations 85
CHAPTER 5 : CORRELATION BETWEEN DEXMEDETOMIDINE, BIOMARKERS AND CLINICAL VARIABLES 87
5.1 Introduction 87
5.1.1 Relationship between variables 87
5.1.1.1 Perioperative dexmedetomidine 87
5.1.1.2 Length of hospitalisation 87

5.1.1.3 ICU length of stay 87
5.1.1.4 Aortic cross-clamp time 87
5.1.1.5 Cardiopulmonary bypass time 87
5.1.1.6 Hs-cTnT at 24 hours 88
5.1.1.7 CRP 89
5.1.1.8 NT-proBNP 89
5.2 Discussion 89
5.2.1 Dexmedetomidine 89
5.2.2 Preoperative hs-cTnT 89
5.2.3 24-hour hs-cTnT 90
5.2.4 Aortic cross-clamp time 91
5.2.5 Cardiopulmonary bypass time 91
5.2.6 ICU length of stay 92
5.2.7 Length of hospitalisation 92
5.3 Conclusions and recommendations 92
5.4 Limitations 93
CHAPTER 6 : DEXMEDETOMIDINE AS A PREDICTOR OF ADVERSE OUTCOME .. 94
6.1 Introduction 94
6.1.1 ICU stay as the outcome variable 94
6.1.2 Hospital stay as the outcome variable 95
6.1.3 Thirty-day mortality as an outcome variable 100
6.2 Discussion 102
6.2.1 Association between dexmedetomidine and outcome 102
6.2.2 Age as a predictor of outcome 103
6.2.3 Ejection fraction as a predictor of outcome 103
6.2.4 NT-proBNP as a predictor of outcome 103
6.2.5 Hs-cTnT as a predictor of outcome 104
6.2.6 Aortic cross-clamp time as a predictor of outcome 104
6.3 Conclusions 105
6.4 Recommendations 106
6.5 Limitations 106
CHAPTER 7 : ETHNICITY, GENDER, CORONARY ARTERY DISEASE AND RISK FACTORS 107

7.1 Introduction 107
7.1.1 General Characteristics and Demographic Profile 107
7.1.2 Cardiovascular Risk Factors 110
7.1.3 Ethnic and Gender Comparison 111
7.2 Discussion 116
7.2.1 Ethnicity and coronary artery disease 116
7.2.2 Risk factor profile 118
7.2.2.1 Hypertension 118
7.2.2.2 Obesity 119
7.2.2.3 Dyslipidaemia 120
7.2.2.4 Diabetes mellitus 120
7.2.2.5 Smoking 120
7.2.2.6 Number of risk factors 121
7.2.2.7 Age and gender 121
7.3 Conclusions and recommendations 121
7.4 Limitations 122
CHAPTER 8 : DEXMEDETOMIDINE PHARMACOETHNICITY 123
8.1 Introduction 123
8.1.1 Baseline Characteristics 123
8.1.2 Postoperative ethnic and gender comparisons 126
8.2 Discussion 129
8.3 Limitations 130
CHAPTER 9 : THE INFLUENCE OF DEXMEDETOMIDINE ON TROPONIN CHANGES: A SYSTEMATIC REVIEW OF RANDOMISED CONTROLLED TRIALS 131
9.1 Introduction 131
9.2 Background 132
9.3 Methods 133
9.3.1 Literature search 133
9.3.1.1 Search strategy and selection of studies 133
9.3.1.2 Data extraction and quality assessment 133
9.3.2 Statistical analysis 137
9.3.3 Inclusion and exclusion criteria 137
9.3.4 Primary and secondary data points 138

9.4 Results 138
9.4.1 Analysis of included studies 138
9.4.2 Meta-analysis of the impact of intraoperative dexmedetomidine on outcomes 141
9.4.3 Coronary artery bypass graft subgroup analyses 144
9.5 Reliability of data 145
9.6 Discussion 146
9.7 Conclusion 148
CHAPTER 10 : SUMMARY OF RESULTS 149
10.1 Findings in this current study 149
10.1.1 Addressing the gap in knowledge 149
10.1.2 The impact of dexmedetomidine on outcomes in CABG surgery 149
10.1.3 Pharmacoethnicity 151
10.1.4 Ethnic and gender differences in cardiovascular risk factor profile 151
10.1.5 Meta-analysis of the effects of dexmedetomidine on outcomes in cardiac surgery with a coronary artery bypass graft surgery sub-analysis 152
10.2 Conclusions 152
10.3 Recommendations 153
BIBLIOGRAPHY 155
APPENDICES 191
Appendix 1: Medicines Control Council 191
Appendix 2: Human Research Ethics Committee 192
Appendix 3: Postgraduate Committee 193
Appendix 4: Title Change 194
Appendix 5: Information leaflet and informed consent 196
Appendix 6: Trial Insurance 222
Appendix 7: Consort Checklist 223
Appendix 8: PRISMA Checklist 226
Appendix 9: Turnitin Report 228

TABLE OF FIGURES

Figure 1.1: Life expectancy in optimistic and pessimistic scenarios 2

Figure 1.2: Global deaths by disease groups 3

Figure 2.1: CPB inflammatory response 15

Figure 2.2: Troponin wash-in and wash-out curves 19

Figure 3.1: CONSORT randomisation flow chart 60

Figure 4.1: Patients on cardiovascular medical therapy 61

Figure 4.2: Comparison between dexmedetomidine and placebo 63

Figure 7.1: Proportional representation of different ethnic groups 108

Figure 7.2: Comparison of proportions of patients on myocardial protective cardiovascular medical therapy by population group 109

Figure 7.3: Stratification of patients according to body mass index classification 110

Figure 7.4: A comparison of risk factor profiles by ethnic group 111

Figure 9.1: PRISMA 2009 flow diagram 136

Figure 9.2: Analysis of cTn change 24 hours (ng/ml) 142

Figure 9.3: Analysis of CKMB change 24 hours (ng/ml) 142

Figure 9.4: Analysis of TNFα change 24 hours (pg/ml) 142

Figure 9.5: Analysis of IL-6 change 24 hours (pg/ml) 142

Figure 9.6: Analysis of length of stay in ICU (hours) 143

Figure 9.7: Analysis of length of stay in ICU (days) 143

Figure 9.8: Analysis of length of stay in hospital (days) 143

Figure 9.9: Analysis of short-term mortality 143

Figure 9.10: Analysis of long-term mortality 143

Figure 9.11: Funnel plot: length of hospital stay (days) 144

Figure 9.12: Analysis of cTn change 24 hours coronary subgroup (ng/ml) 144

Figure 9.13: Analysis of CKMB change 24 hours coronary subgroup (ng/ml) 145

Figure 9.14: Analysis of length of stay in ICU coronary subgroup (hours) 145

Figure 9.15: Analysis of length of stay in ICU coronary subgroup (days).....145

Figure 9.16: Analysis of length of stay in hospital coronary subgroup (days) 145

LIST OF TABLES

Table 2.1: Randomised controlled studies of dexmedetomidine in CABG surgery 42

Table 4.1: Characteristics differences between dexmedetomidine and placebo..... 62

Table 4.2: Troponin at baseline and 24 hours..... 63

Table 4.3: Comparison between IL-6 and IL-10 at 24-hour postinduction between dexmedetomidine and placebo..... 64

Table 4.4: Length of stay in ICU and hospital..... 65

Table 4.5: Adverse events by drug..... 67

Table 5.1: Correlation between dexmedetomidine administration, biomarkers and clinical variables..... 88

Table 6.1: Simultaneous quantile regression model for LOS in ICU – Model 1..... 96

Table 6.2: Simultaneous quantile regression model for LOS in ICU – Model 2..... 97

Table 6.3: Simultaneous quantile regression model for hospital stay – Model 1 98

Table 6.4: Simultaneous quantile regression model for hospital stay – Model 2 99

Table 6.5: Exact logistic regression for 30-day mortality 101

Table 6.6: Exact logistic regression for 30-day mortality 102

Table 7.1: Classification of patients according to the WHO obesity and BMI classification 109

Table 7.2: A comparison of basic characteristics between three ethnic groups 112

Table 7.3: A comparison of basic characteristics between Africans and a Combined group.113

Table 7.4: A comparison of biomarker profiles between three ethnic groups.....114

Table 7.5: A comparison of biomarker profiles between Africans and the Combined group 114

Table 7.6 A comparison of basic characteristic differences between males and females 115

Table 8.1: Dexmedetomidine group by ethnicity – baseline data 124

Table 8.2: Non-dexmedetomidine group by ethnicity – baseline data.....124

Table 8.3: African patients by drug – baseline data 125

Table 8.4: Dexmedetomidine group by gender – baseline data 126

Table 8.5: Dexmedetomidine group by ethnicity – postoperative data 127

Table 8.6: Non-dexmedetomidine group by ethnicity – postoperative data 127

Table 8.7: Postoperative parameters between dexmedetomidine and non-dexmedetomidine groups among African patients 128

Table 8.8: Postoperative parameters in the dexmedetomidine group according to gender 128

Table 9.1: Methodological quality assessment of trials by author 140

Table 9.2: Characteristics of enrolled studies 141

LIST OF ABBREVIATIONS

ACE	angiotensin converting enzyme
ASA	acetylsalicylic acid
Aocx	aortic cross-clamp
AKI	acute kidney injury
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BBB	bundle branch block
BIS	bi-spectral index sensor
BMI	body mass index
CAD	coronary artery disease
CABG	coronary artery bypass graft
CCF	congestive cardiac failure
CHBAH	Chris Hani Baragwanath Academic Hospital
CKMB	creatinine kinase muscle and brain
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CPB	cardio pulmonary bypass
CRP	C-reactive protein
cTn	cardiac troponin
cTnT	cardiac troponin T
cTnI	cardiac troponin I
CVD	cardiovascular disease
dP/dtmax	rate of rise of left ventricular pressure
ECG	electrocardiogram
ECC	extra corporeal circulation
ECMO	extracorporeal membrane oxygenator
EF	ejection fraction
ELISA	enzyme linked immunosorbent assay
GBD	global burden of disease
HJAH	Helen Joseph Academic Hospital
hs-cTn	high-sensitivity cardiac troponin
hs-cTnT	high-sensitivity cardiac troponin T
hs-cTnI	high-sensitivity cardiac troponin I
HREC	Human Research Ethics Committee

IABP	intra-aortic balloon pump
ICU	intensive care unit
IHD	ischaemic heart disease
IL	interleukin
IPC	induced ischaemic episodes
KDIGO	kidney disease improving global outcomes
KET-DEX	ketamine-dexmedetomidine
LAD	left anterior descending artery
LVEDP	left ventricular end-diastolic pressure
LVEF	left ventricular ejection fraction
Lido-DEX	lignocaine-dexmedetomidine
LOS	length of stay
MAC	mean alveolar concentration
MACE	major adverse cardiac events
MACCE	major adverse cardiac and cerebral events
MCC	Medicines Control Council
MI	myocardial infarction
NHLS	National Health Laboratory Service
NO	nitric oxide
NOc	nitric oxide constitutive
NOi	nitric oxide inducible
NSTEMI	non-ST elevation myocardial infarction
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
OPCAB	off-pump coronary artery bypass
PSM	propensity score matching
PURE	prospective urban rural epidemiology
RCT	randomised controlled trial
SIRS	systemic inflammatory response syndrome
STEMI	ST elevation myocardial infarction
SVRI	systemic vascular resistance index
TIVA	total intravenous anaesthesia
TEA	thoracic epidural anaesthesia
TNF-α	tumour necrosis factor alpha

WHO	World Health Organization

CHAPTER 1 : INTRODUCTION

1.1 Background and rationale of the study

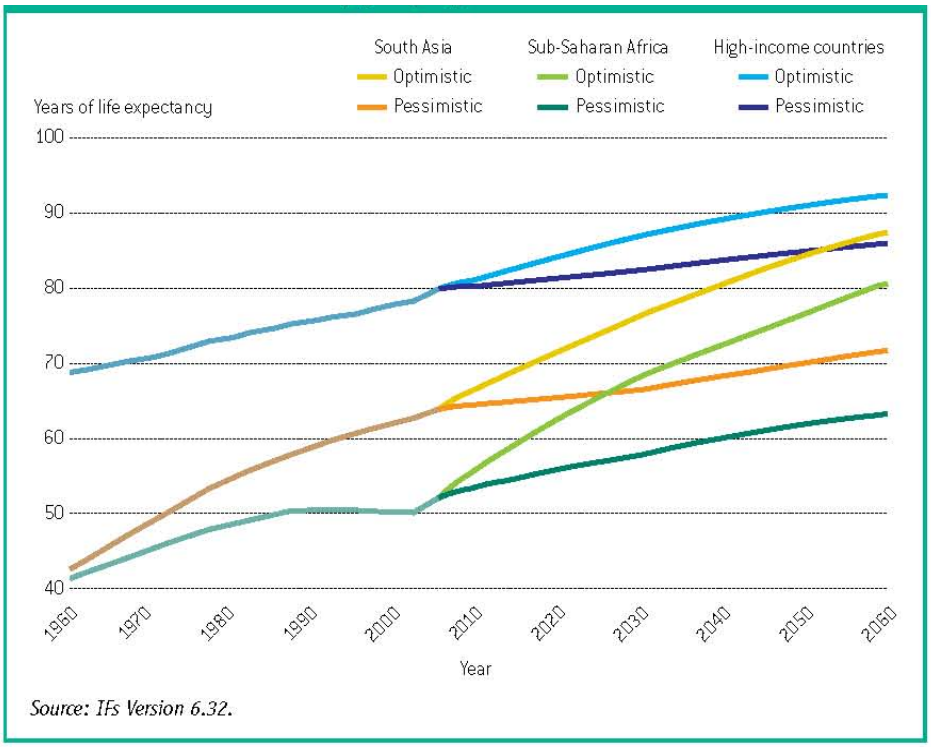
Coronary artery disease (CAD) is a debilitating disease associated with increased morbidity, multi-organ dysfunction and death (1). Coronary artery bypass graft (CABG) surgery, a procedure undertaken to alleviate the occlusion in the coronary arteries, especially in those patients where medical therapy and other interventional procedures have been exhausted, is also associated with major complications (2). A multidisciplinary approach towards reducing morbidity and mortality in these patients continues (3). Surgical options such as off-pump coronary artery bypass (OPCAB) surgery and mini-cardiopulmonary bypass (mini-CPB) surgery are being utilised (4).

Anaesthetic means of reducing the effects of the inflammatory response are continuing to be investigated (5-7). Newer drugs are being tested to assist in the alleviation of the stress response to CPB (8). Dexmedetomidine, an alpha agonist, has the hallmarks of a suitable agent to match some of the characteristics anaesthesiologists are looking for to achieve myocardial protection during CABG surgery (9-14).

There have been numerous studies in noncardiac surgery suggesting the positive effects of this drug towards myocardial protection, whereas not enough evidence exists in CABG surgery (10). The results of noncardiac surgery trials cannot necessarily be extrapolated to patients presenting for CABG surgery. The latter not only experience ischaemia-reperfusion, they also experience increased levels of inflammatory response due to the interaction of blood with the CPB circuit (15). Therefore, this randomised controlled trial was undertaken to investigate the effects of dexmedetomidine on ischaemic and inflammatory biomarkers in patients undergoing CABG surgery. Furthermore, the study sought to determine if these effects would translate into clinical benefits by reducing ICU length of stay (LOS), duration of hospitalisation, and 30-day mortality in patients undergoing CABG surgery.

1.2 The epidemiology of coronary artery disease

Cardiovascular disease (CVD) has been found to be a leading cause of death in the Global Burden of Disease (GBD) study (16) of the World Health Organization (WHO) (17). It was found to lead to 12.2% of all deaths annually, globally with variability between income groups (16). CVD contributed 9.4%, 13.9% and 16.3% of mortality in low-, middle- and high-income countries, respectively. CVD came second to respiratory and cerebrovascular disease in the low- and middle-income countries, respectively (16).

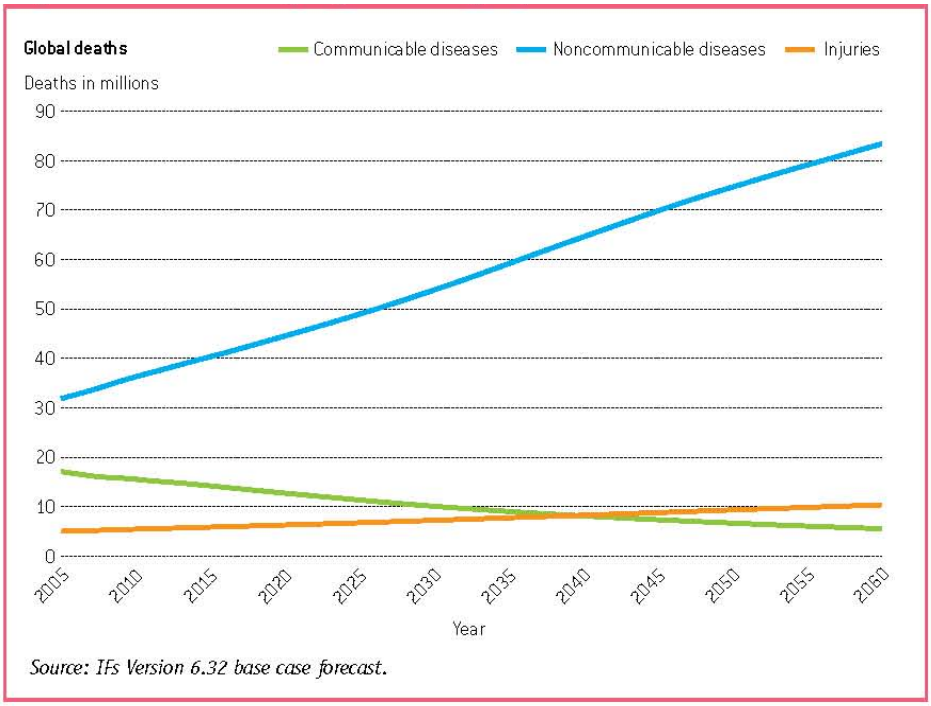


With permission from R Kuhn (18). This figure is copied in terms of Section 12 (Fair Dealing) of the SA Copyright Act No. 98 of 1978 (as amended).

Figure 1.1: Life expectancy in optimistic and pessimistic scenarios

According to projections by the WHO, ischaemic heart disease will be the leading cause of death by 2030 (16). It is estimated that in 2020, CAD will be responsible for approximately 11 million deaths globally (19). CVD was also projected to become the cause of most deaths in all income countries in 2002 to 2030, and 2005 to 2060 projections (Figures 1.1 and 1.2) (18, 20, 21).

Earlier studies in South Africa had shown the prevalence of CAD in Africans to be very low (22, 23). CAD was believed to be of low prevalence in the sub-Saharan regions of the continent until the late 1990s (24). While the incidence and disease pattern among Europeans and Asians in Africa mirrored those of international communities, the disease was found to be rare in Africans in South Africa in the 1970s (22). A slow increase in the prevalence of CAD in this ethnic group has been observed, possibly as a result of migration, urbanisation and disease progression (25-27) .



With permission from R Kuhn (18). This figure/image is copied in terms of Section 12 (Fair Dealing) of the SA Copyright Act No. 98 of 1978 (as amended).

Figure 1.2: Global deaths by disease groups

Risk factors for CAD such as obesity, high cholesterol, diabetes, smoking and hypertension have been on the rise (28, 29) among Africans in South Africa. There are no studies that look at patients undergoing CABG in urban state hospitals in South Africa or sub-Saharan Africa.

This current study details the characteristics of the different ethnic groups and their risk factor profile compared with earlier reported studies. The pharmacoethnicity of dexmedetomidine, in relation to biochemical and clinical outcomes, was also investigated.

1.3 Inflammation and the stress response to surgery

Occlusive CAD leads to an imbalance in oxygen supply–demand to the myocardium (30, 31). Patients presenting for CABG surgery have a higher burden of ischaemia at presentation. This puts them at higher risk of morbidity and mortality than other patients (32). Most patients in this current study presented with risk factors such as diabetes mellitus, obesity, hypertension, and smoking that resulted in a chronic state of inflammation (24, 29).

CABG surgery with CPB elicits a much higher degree of neuro-humoral and inflammatory response than OPCAB or mini-CPB (33, 34). The neuro-humoral response incorporates activation of the sympathetic nervous system, the pro-inflammatory and the anti-inflammatory systems (35), resulting in the simultaneous release of catabolic and immunosuppressive hormones (35-39). Equally eliciting the stress response during CABG surgery, are the following factors: exposure of blood cells to the negatively charged surface of the CPB; the non-physiological circulation; non-pulsatile nature of the CPB; blood transfusion; hypothermia; and ischaemia-reperfusion (36-38).

The surgical stress response is mediated through the sympathetic autonomic system (31, 38). Activation leads to stimulation of the adrenal medulla and release of noradrenaline from presynaptic nerve endings (38). Catecholamine release leads to sheer stress in the already compromised coronary vasculature (31). Plaque fissuring and rupture often ensue (31).

A hypercoagulable state increases the risk of coronary thrombus formation (35, 36). This is a result of upregulation of coagulation and platelet function, and the down-regulation of fibrinolysis (36). Endothelial injury during CPB occurs due to damage to blood constituents, subsequent expression of tissue factor and platelet activation (40). Venous graft occlusion is the highest risk during this period (40).

1.4 Myocardial ischemia-reperfusion injury

Anaerobic glycolysis follows a period of myocardial ischaemia, leading to accumulation of lactate, dihydronicotinamide adenine dinucleotide and hydrogen ions (31, 35, 40). The cellular membrane Na^+/H^+ pump fails, leading to an increase in intracellular Na^+, which drives the Na^+/Ca^{2+} pump. Intracellular Ca^{2+} is increased, the integrity of the membrane lipids fails, and cellular oedema develops (35, 41).

The heart is stopped during CABG surgery on CPB, resulting in accumulation of ischaemic by-products. During aortic unclamping, reperfusion encourages generation of cytotoxic oxygen metabolites and oxygen-free radicals (35, 41-43). The failing heart is unable to respond adequately to these oxygen-free radicals, due to inadequate antioxidant enzymes (35, 41, 42, 44).

Myocardial enzyme leak and its interpretation during CABG is often complicated by the following: the ischaemia-reperfusion; the systemic inflammatory response syndrome (SIRS) response; organ failure; auto-transfusion of shed mediastinal blood; blood transfusion; aortic cross-clamp times and also direct injury to the heart muscle, as occurs with atriotomy (45-49).

The reasons for mortality and morbidity during CABG surgery are multifactorial. These include: haemodynamic instability, graft anatomical and functional failure, myocardial ischaemia during aortic cross-clamping, reperfusion injury, cardioplegia-induced myocardial dysfunction, and activation of the inflammatory and coagulation cascades (35, 40, 42, 44). The highest risk of mortality and morbidity is in the early postoperative period (50, 51). Studies estimate early postoperative myocardial infarction rates of 1%–25%, whilst rates of mortality ranged from 0.5%–14% (52, 53).

Major adverse cardiac and cerebral events (MACCE), together with renal and respiratory dysfunction, are often associated with long waiting periods before surgery (54, 55). An overall death rate of 13.4 deaths or myocardial infarction per 100 patient years, have been found on the awaiting surgery list (56). Patients on the waiting list are at particular risk if they

present with left main disease/severe triple vessel disease, with angina at rest or ST segment changes.

1.5 Myocardial protection

Myocardial enzymes are utilised as markers of myocardial injury during cardiac surgery (49). A proper interpretation of the pattern of enzyme leakage is imperative to allow timeous intervention strategies to be implemented. Echocardiographic evidence used together with clinical findings of low cardiac output can lead to earlier diagnosis leading to goal-directed intervention, and better outcomes (57, 58). Cardiac troponins are used to identify and quantify levels of myocardial injury (45).

There are recommended cut-off points arising from previous studies for myocardial infarction (MI) in the setting of CABG. Currently, CABG-related MI (type 5 MI) is defined as:

"1) an increase in the ischaemic biomarker level more than 10 times the upper reference limit and either new pathological Q waves or new bundle branch block (BBB),
2) new graft or native coronary artery occlusion confirmed angiographically, or
3) imaging evidence of new loss of viable myocardium" (57, 58).

MACCE characterise the complications of myocardial ischaemia and consequent poor tissue perfusion. Multiorgan dysfunction leads to prolonged LOS in ICU and hospital (50). There is an established association between CAD and increased morbidity and mortality (59). The complications can occur from the prediagnosis to the postrevascularisation period (59). Morbidity and mortality are emotionally devastating for the patient, the family and the medical team (35). There are dire financial consequences (51). A multidisciplinary approach is necessary to combat this multifaceted problem in order to improve outcomes.

There is a need for modifications and continued improvement of surgical, anaesthetic, perfusion, and postoperative care strategies (35). There have been numerous interventions targeted at attenuation of the neuro-humoral response (3, 60, 61). Intervention strategies aimed at attenuation of the stress response in CABG surgery patients include: modifications

to the cardiopulmonary bypass machine; modification of cardioplegia solutions; anaesthetic drugs; alternative surgical approaches; and attenuation of the neuro-endocrine response (37, 62, 63). The results from studies investigating these interventions have often been equivocal (3, 64). Sympatho-modulatory therapies, including ß-adrenergic blockers, regional anaesthesia, and α2-adrenergic agonists, are some of the modalities in the anaesthesiologist's armamentarium (65-68).

1.6 Anaesthetic agents and cardiac protection

As with colleagues in the cardiothoracic, perfusion and intensive care disciplines; research continues in anaesthesiology in the pursuit of the ultimate cardioprotective agent (69-74). Volatile and intravenous anaesthetic agents have been examined (3, 75).

Alpha-2 agonists exert their cardioprotective effects by attenuating the release of catecholamines and inhibiting stress-induced tachycardia (49, 76). Their pharmacological actions are mediated via α-2A adrenergic and the imidazole-1 receptors and include lowering of the central sympathetic tone (9, 77). Secondary to their sympathetic effects, they are sedative, anxiolytic and induce analgesia (77, 78). Prejunctional α-adrenergic receptors have α-2B antiadrenergic effects (79). Postjunctional α-2A adrenergic receptors in neurons localised in the locus coeruleus and nucleus reticularis lateralis act via inhibition of L-type Ca^{2+} channels, to confer anaesthetic and short-term hypertensive effects (79).

Pharmacological agents in this group available to anaesthesiology are clonidine, mivazerol and the newer dexmedetomidine (10, 79, 80). Dexmedetomidine is an α-2 agonist with analgesic and sedative effects. Due to its actions on the stress response, it presents itself as a possible intervention strategy in myocardial protection (81-83). This current study aimed to investigate the effects of intraoperative dexmedetomidine on myocardial protection in CABG surgery.

1.7 Pharmacoethnicity

The literature suggests evidence of ethnic influence on disease prevalence (84-88). Studies have shown ethnic and gender differences in disease prevalence and risk factors profile of patients (89-92). Genetic variability, linked to ethnicity, is known to have a relationship with pharmacogenetics and pharmacogenomics (93-95). Drug metabolism, transport proteins and drug target sites are some of the areas where these differences manifest (93). Although the field of study is still new and sample sizes in the reported studies were small, there is evidence of the influence of ethnicity on the pharmacological effects of dexmedetomidine (96, 97). A subanalysis of data in this current study was undertaken to investigate the effect of ethnicity on disease prevalence and dexmedetomidine pharmacodynamics. We sought to investigate the effects of pharmacoethnicity on biomarkers hs-cTnT, CRP and interleukins.

1.8 Aims of the study

The primary aim of this study was to investigate the cardioprotective effects of dexmedetomidine on myocardial injury as reflected by: 24-hour myocardial ischaemic biomarker – serum high-sensitivity cardiac troponin T (hs-cTnT).

1.9 Objectives of the study

The objectives of this study were to investigate:

- The effects of dexmedetomidine on: cardiac ischemic markers 24 hours post anaesthetic induction in patients undergoing CABG surgery; inflammatory markers; LOS in ICU; length of hospitalisation; and mortality.
- To determine the role of pharmacoethnicity on the effects of dexmedetomidine on ischaemic biomarker outcomes post CABG surgery together with the ethnic differences in the prevalence of CAD and its risk factors.

1.10 Project outline

1.10.1 Hypothesis

In patients undergoing CABG surgery on CPB, dexmedetomidine protects the myocardium from ischaemic injury as evidenced by lower levels of ischaemic and inflammatory

biomarkers such as hs-cTnT, IL-6 and IL-10. This translates into shorter LOS in ICU, shorter length of hospitalisation and lower mortality.

1.10.2 Demarcation of the study

The study was conducted at the Charlotte Maxeke Johannesburg Academic Hospital's (CMJAH) cardiothoracic unit. This is the only state hospital in Johannesburg providing cardiothoracic services.

1.10.3 Study population

Consecutive consenting patients with triple vessel or left main stem CAD undergoing on-pump CABG surgery at the CMJAH were recruited for this current study. The study was conducted in accordance with the Declaration of Helsinki (98).

1.10.4 Ethical considerations

Ethical approval to conduct the study was obtained from the University of Witwatersrand Human Research Ethics Committee (HREC). Permission to use dexmedetomidine for this purpose was obtained from the Medicines Control Council (MCC) of South Africa. Written informed consent was obtained from each patient prior to enrolment in the study.

All study patients were covered with a trial insurance procured from the university. Both patients and the clinicians involved in the care of the patients were blind to the drug (dexmedetomidine or saline) that was administered. A randomised controlled trial (RCT) was undertaken. Randomisation was performed by the pharmacist who prepared the drug to be administered to the patient.

A list from 1 to 90 was prepared before the study commenced. Forty five dexmedetomidine and 45 placebo entries were randomly assigned. As patients were enrolled, the pharmacist allocated them into consecutive numbers and prescribed and prepared the blinded randomly assigned drug. The drug was treated by the clinicians as though it was dexmedetomidine and administered in the recommended dosage of 0.3–0.7 μg/kg/h, depending on the patient's haemodynamic status, and supplemented with opioid analgesics.

1.10.5 Research methodology

1.10.5.1 Study design

The study was a prospective double-blind, randomised, placebo-controlled investigation. A standardised anaesthetic technique was performed for all patients in both arms of the study.

1.10.5.2 Inclusion criteria

a. Left main or triple vessels coronary artery disease

b. Age above 18 and below 65 years

1.10.5.3 Exclusion criteria

a. Age below 18 or above 65 years.

b. Pregnancy or lactation.

c. Liver dysfunction aspartate transaminase (AST) or alanine transaminase (ALT) > twice the upper range of normal). (Normal values NHLS: AST 5 – 40 and ALT 5 – 56 units/L).

d. Sick sinus syndrome.

e. Concurrent use of medication with potential for major drug interactions such as propoxyphene, sodium oxybate and tinazide.

f. Patients requiring preoperative inotropic support.

g. Asthma.

h. Uncontrolled pulmonary congestion.

i. Evidence of ongoing infection.

1.10.5.4 Primary outcome

1. Postoperative serum hs-cTnT measured 24 hours postinduction.

1.10.5.5 Secondary outcomes

1. The effects of dexmedetomidine on serum hs-cTnT, IL-6 and IL-10, measured at

induction and 24 hours postinduction.

2. The effects of dexmedetomidine on length of ICU stay in days.
3. The effects of dexmedetomidine on length of hospitalisation in days.
4. The effects of dexmedetomidine on 30-day postoperative mortality.
5. The role of pharmacoethnicity on the effects of dexmedetomidine on biomarkers (hs-cTnT; IL-6; IL-10); length of ICU stay; length of hospitalisation; and 30-day mortality.

1.10.6 Blood sample analysis

Blood samples stored were stored at –80°C and analysed in batches.

1.10.7 Statistical analysis, sample size and power estimates

1.10.7.1 Sample size and power estimates

From previous studies (99, 100), the study estimated the mean cardiac troponin T (cTnT) levels of 1.3 and 0.4 ng/mL with a standard deviation of 1.5 ng/mL in each arm (placebo vs. dexmedetomidine, respectively). The study assumed that a two-tailed t-test, at $\alpha = 0.05$ for independent samples would be used to compare mean troponin levels in the 2 groups (dexmedetomidine vs. placebo). Assuming these estimates, a minimum sample size of 40 per arm in order to achieve a power of 80.4%, was estimated. To allow for dropouts, five patients were added to each arm of the study.

1.10.7.2 Statistical analysis

Data was analysed using Stata [Stata Corp LP Statistics/Data Analysis Copyright 1985 – 2013 Stata Corp 4905 Lakeway Drive Special Edition College Station, Texas 77845 USA 800–STATA]. Categorical and continuous variables were compared using Chi-squared and Student's t-tests, respectively. Analysis of normally distributed data was performed using the mean and standard deviation, whereas the median and interquartile range were used for skewed data.

Comparative statistics were used to analyse the two study subsets using paired and unpaired Student's t-tests for parametric data, or Mann-Whitney and Wilcoxon matched pairs for nonparametric data. Anova and Kruskal Wallis tests were used to compare three and more, normally distributed and skewed data sets, respectively. Correlations were determined by Pearson and Spearman tests for parametric and nonparametric data respectively. Categories were plotted on a contingency table and analysed as proportions using the Fisher's exact test.

Univariate and multivariate regression analysis of outcome measures with independent variables were analysed. Categorical outcome measures were analysed using logistic regression. Diagnostics for the regression models and transformation of data were performed where indicated. P values < 5% were considered significant.

1.11 Significance of the study

Very few studies have looked at the effects of dexmedetomidine in CABG surgery. Of those that did, modalities such as OPCAB and mini CPB were used instead of full CPB (101, 102). Additional forms of anaesthetic myocardial protection were used (101, 102). We did not find a study assessing the role of ethnicity on the effects of dexmedetomidine on ischaemic markers; inflammatory markers; duration of ICU stay; length of hospitalisation; or mortality.

1.12 Potential limitations

The limitations in this study were the lack of financial resources to do all the assays we had proposed to do such as plasma levels of drugs and their pharmacokinetics and pharmacodynamics, and postoperative biomarkers pro b-type natriuretic peptide (proBNP) and c-reactive protein (CRP).

1.13 Thesis outline

This thesis is presented as follows:

Chapter 1: an introduction into epidemiological, pathophysiological and myocardial protection aspects of CAD; a brief summary of the project outline.

Chapter 2: a review of the literature on myocardial ischaemia, myocardial protection,

myocardial protection pharmacotherapy and the effects of dexmedetomidine on outcomes in CABG surgery; a review of the literature on the effects of ethnicity on CAD in South African and sub-Saharan African countries; the role of pharmacoethnicity on the effects of dexmedetomidine on outcomes.

Chapter 3: study methods.

Chapter 4: results, discussion and conclusions on the effects of dexmedetomidine in CABG surgery.

Chapter 5: results, discussion and conclusions on the correlation between dexmedetomidine, postoperative biomarkers and clinical outcomes.

Chapter 6: results, discussion and conclusions of a multivariate analysis, for determination of an association between dexmedetomidine and other variables, with outcomes post-CABG surgery.

Chapter 7: results, discussion and conclusions on ethnicity and CAD.

Chapter 8: results, discussion and conclusions on dexmedetomidine and pharmacoethnicity.

Chapter 9: systematic review and meta-analysis of the impact of dexmedetomidine on outcomes in cardiac surgery with a subanalysis of CABG surgery patients.

Chapter 10: summary of the results and recommendations.

CHAPTER 2 DEXMEDETOMIDINE, BIOMARKERS AND CLINICAL OUTCOMES

2.1 Literature review

2.1.1 Background

This section covers a review of the literature undertaken to understand the following processes during CABG surgery: myocardial ischaemic markers and their interpretation; inflammatory markers; myocardial protection; anaesthetic agents and myocardial protection; α-2 agonists and myocardial protection; dexmedetomidine pharmacology.

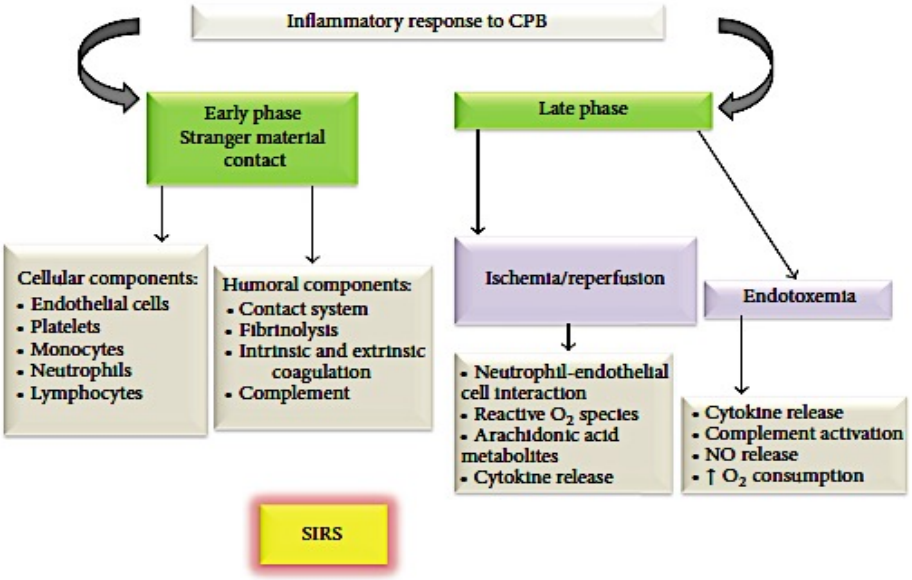
A literature review was undertaken to highlight the following: anaesthetic agents and myocardial protection; insight into the choice of drugs made in designing this current study. A literature review detailing the effects of dexmedetomidine on myocardial protection in preclinical and noncardiac studies that contributed to the conceptual framework of this current study was undertaken.

The literature on the effects of dexmedetomidine on ischaemic markers, inflammatory markers, morbidity and mortality after CABG surgery, is reviewed in depth. An analysis of the literature is also undertaken detailing the differences between this current study and previous studies on the use of dexmedetomidine in CABG surgery. The literature review of studies on the association of dexmedetomidine and outcome variables was undertaken.

2.1.2 Inflammatory markers in cardiac patients

The extracorporeal surface of CPB induces contact activation. It initiates the coagulation system leading to clot formation and activation of the complement system (103). Contact activation leads to anaphylaxis and chemotaxis (103). Complement activation induces the synthesis of pro-inflammatory and anti-inflammatory cytokines. The balance between the activity of the pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-8 (IL-8), tumour necrosis factor alpha (TNF-α) and interleukin-1 (IL-1), and anti-inflammatory

cytokine interleukin-10 (IL-10), determine the level of inflammatory response (Figure 2.1) (6, 104-106).



Adapted from Bulow *et al.* (8). This figure is copied in terms of Section 12 (Fair Dealing) of the SA Copyright Act No. 98 of 1978 (as amended).

Figure 2.1: CPB inflammatory response

Patients undergoing CPB are prone to developing endotoxaemia. Endotoxin stimulates the formation of IL-6 and, by binding to human serum protein, enhances TNF-α production (6, 104, 105). Anaesthetic agents, through their influence on and modification of intercellular communications, alter the response to surgical stress (36, 103, 107).

Pro-inflammatory cytokines and endotoxins lead to the production of inducible nitric oxide (NOi) (8, 108, 109). The NOi increases vascular permeability and vasodilation, which may result in poor cardiac output and capillary leak in the postoperative period. The release of constitutive nitric oxide (NOc), which has a protective role, is impaired after CPB (8, 108, 109). Inhibition of this protective nitric oxide (NO) may lead to vasoconstriction.

Vasoconstriction, together with microaggregates formed by activated leukocytes and platelets, may lead to microvascular occlusion. Packed red cells and blood components are essential for their oxygen-carrying capacity, volume support, and haemostasis (8, 108, 109). They are, however, associated with immuno-modulation that may contribute to ensuing multiorgan failure (8, 108, 109).

This current study sought to investigate the effects of dexmedetomidine on pro-inflammatory and anti-inflammatory mediators (IL-6 and IL-10).

2.1.3 Myocardial ischaemic markers

In 90% of cardiac surgery patients, cardiac enzymes are elevated within 24 hours (35, 110). Atriotomy and ischaemia-reperfusion are major contributors. Cardiac troponins T and I (cTnT and cTnI), belong to the thin filament regulatory system of the myocardial contractile complex (35, 111). These proteins are expressed in the human myocardium, and not in extracardiac tissues such as skeletal muscles. This allows for more accurate interpretation of laboratory values. Compared with creatinine kinase muscle and brain (CKMB), cardiac troponin (cTn) enzymes are more specific and sensitive to myocardial injury, and are not confounded by injury in remote tissues (111).

Abramov *et al.* (45) showed that troponins have a short half-life in the myocardium during ischaemia, due to progressive intracellular degradation. They found that: "for preservation and enhanced sensitivity, the enzymes are released as complexes, viz. troponin I–troponin C, troponin I–troponin T, troponin I–troponin T and C covalent complexes. Troponin covalent complexes of troponin T and C appear with mild ischaemia, and disappear with more severe injury. The elimination of these enzymes takes place in the liver, pancreas, kidney and reticuloendothelial system. Multiorgan failure may lead to prolonged increases and impaired clearance." (35, 45)

A strong correlation between troponin levels, myocardial injury, morbidity and mortality in acute coronary syndrome, has been established (45, 111, 112). Postoperatively, cTn values

were found to be a strong predictor of in-hospital death and major postoperative complications in a group that included high-risk patients (46). Lasocki *et al.* (46) found that postoperative cTnI of 13 ng/ml was a cut-off point and an independent predictor of in-hospital death.

Similarly, Jacquet *et al.* (119) found that cTnI levels of 13.4 ng/ml after CABG surgery differentiated between patients with perioperative MI/ischaemia and those with uneventful outcome. Fellahi *et al.* (113) found the best cTnI cut-off value to be between 12.1 and 13.4 ng/ml. This closely resembled values described by other investigators (46) 119). They found that with an increase of greater than 40 ng/ml, in-hospital mortality reached 44% (113).

High cTnI values were associated with a 37-fold increase in risk of death within 2 years. In a cohort of low preoperative risk patients, a 2-year mortality rate of 4% from MI, congestive cardiac failure (CCF), and sudden death was associated with raised troponin levels (114). Mortality rate was found to be 18% in patients with high cTnI (120). The enzyme washout curve, due to early benign injury, depended on organ function. No significant troponin contribution from defibrillation was found when the type of surgery was considered (112). CABG had the lowest level of troponin leak/release of all surgeries that needed direct myocardial incisions (115, 116).

Domanski *et al.* (112, 115) in their analysis of 7 studies, looked at the association between cardiac enzyme levels in the first 24 hours postsurgery and immediate, short-term and long-term risk of mortality. For all CKMB and troponin ratios (24 hours/preoperative) greater than 1, there was a strong graded independent association with mortality. Abramov *et al.* (45) looked at 9 studies and analysed the elimination curves of troponin. The pattern of increase in plasma troponin levels in cardiac surgery was evaluated through wash-in and wash-out curves of troponin postsurgery and post-MI (45). The post-MI levels were evaluated with and without reperfusion (45).

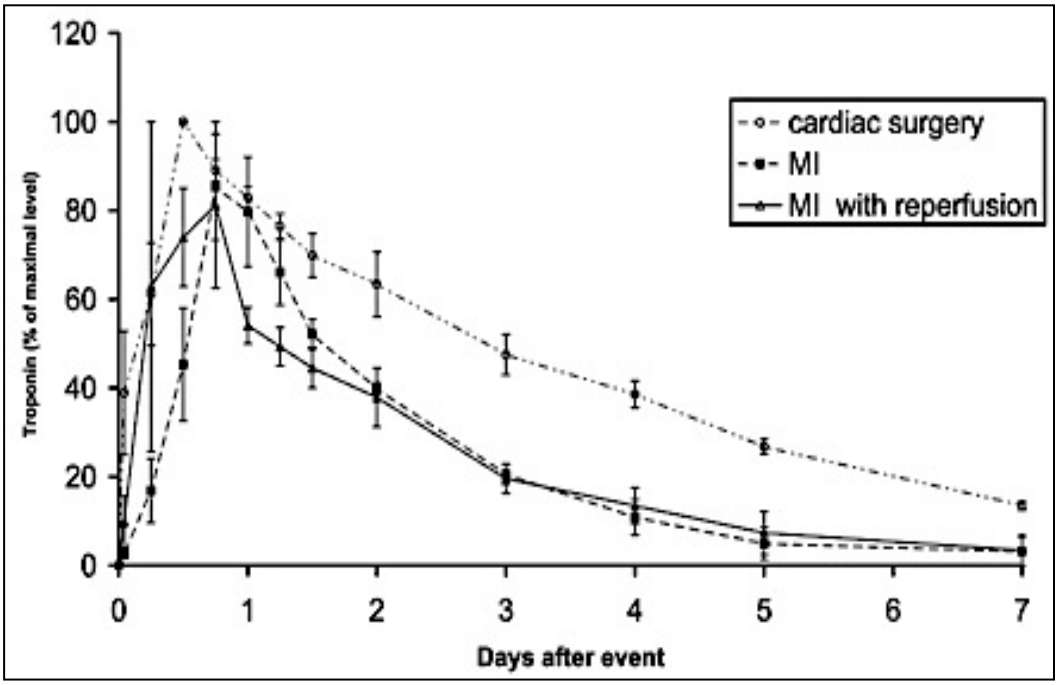
The results were suggestive of differing pathophysiological mechanisms (45). The evaluation of the wash-in and wash-out curves of troponin postsurgery and post-MI showed that the upslope postcardiac surgery was steeper than post-MI, and even steeper than post-MI with reperfusion (Figure 2.2) (47). The downslope postcardiac surgery was less steep with cardiac surgery than post-MI and post-MI with reperfusion. The slow washout was thought to be because ischaemic insult after surgery was milder and more transient than post-MI. Troponin appeared as complexes, rather than in free form, rendering it less vulnerable to degradation (41, 45, 111, 112). Slower elimination after cardiac surgery was also attributed to altered organ functions (41, 42, 45).

The fast peak observed with surgery was suggested to be due to enhanced cell membrane permeability from cellular oedema, rather than permanent cellular damage, as seen in MI (45, 114). Perioperative MI leads to Troponin level peak at 18 to 24 hours postevent as compared with an earlier peak with benign injury (38, 45, 115). Fellahi *et al.* (114, 117) further suggested that a single 24-hour troponin measurement provided an accurate prediction of outcome. This was without having to perform kinetic perioperative enzyme analyses that provided an integrated area under the curve and peak values.

The predictive value of cTn was further confirmed by Thielmann *et al.* (118) who investigated a patient group that was operated on 24 hours after onset of ischaemic symptoms. These patients were labelled as emergency CABG (118). Preoperative cTnI measurement in emergency CABG surgery was found to be an independent predictor of in-hospital mortality and major adverse cardiac events (MACE), as evidenced by ST elevation MI (STEMI) and non-ST elevation MI (NSTEMI) (118).

Nagurney *et al.* (119) found the sensitivity of troponin to be higher six or more hours after the onset of symptoms in patients that presented to the operating theatre. Crescenzi *et al.* (120) found that in CABG surgery, due to atriotomy and stunning, there was much more myocardial damage than with OPCAB, and therefore much higher cTnI concentrations postoperatively. No reperfusion injury occurred during OPCAB due to continued coronary perfusion in a

beating heart. CPB led to the release of at least 2 ng/ml of troponin from atriotomy and inflammation-reperfusion injury (112).



Adapted from Abramov *et al.* (45). X axis – cTn levels in ng/ml. This figure is copied in terms of Section 12 (Fair Dealing) of the SA Copyright Act No. 98 of 1978 (as amended).

Figure 2.2: Troponin wash-in and wash-out curves

Croal *et al.* (47) found a relationship between the number of grafts and the level of cTnI release, with troponin release increasing from 0.22 (0.01 – 1.04) ng/ml with one graft, to 2.78 (1.76 – 5.29) ng/ml with more than three grafts. Troponin levels in their study were found to be predictors of mortality in single, isolated CABG surgery at 30 days, but not at one or three years. Greenson and colleagues (111) established a strong correlation between red blood cell units transfused with peak cTnI. They too found a strong correlation with MACE. Troponin levels were higher and peaked later in those that had significant cardiac events compared with those with minor cardiac events in their study (111).

New wall motion abnormalities were seen at peak values of 40–60 ng/ml troponin concentration. In their meta-analysis, Lurati Buse *et al.* (121) described a significant association between cTn release and mid- and short-term all-cause mortality. Levels exceeding a certain concentration meant more severe, irreversible myocardial damage leading to adverse outcomes (121).

High-sensitivity cardiac troponin (hs-cTn) was found to have a higher sensitivity than conventional cardiac troponin (cTn) in diagnosis of MI (122). In a prospective multicentre study, Rubini Gimenez *et al.* (122) compared hs-cTnT to high-sensitivity cardiac troponin I (hs-cTnI) and found that they are comparable in diagnostic accuracy for NSTEMI (122). However, they found that hs-cTnT was more accurate when the onset of ischaemia was more than three hours prior to testing. Haaf *et al.* (123) found the initial presentation of hs-cTnT to be more accurate in prediction of long-term mortality when compared with hs-cTnI (123).

In this current study, hs-cTnT was measured. According to the Third Universal Definition of Myocardial Infarction expert consensus document, "10 times the upper recommended limit of cTn, in addition to electrocardiographic, angiographic and echocardiographic evidence of ischaemia, should be used for diagnosis of perioperative MI" (57). The imaging and electrocardiographic techniques were not utilised in this current study.

2.1.4 Myocardial protection during cardiac surgery

Myocardial protection during CABG surgery is a challenging phenomenon. The literature on strategies of attenuation of the consequences of the neuro-humoral and ischaemia-reperfusion responses, are summarised in this section and include the following:

The neuroendocrine intervention strategies have included: a focus on cell activation prevention; removal of pro-inflammatory mediators by haemofiltration; use of free radical scavengers; and complement, endotoxin and cyclooxygenase inhibition (49). The sympatho-modulatory therapies, including β-blockers, regional anaesthesia and α2-adrenergic agonists, have been extensively investigated in previous studies (44, 62, 80, 124, 125).

The stress response during minimal extracorporeal circuits (ECCs), such as mini-CPB, and OPCAB have been extensively compared with that during CABG with CPB (126). OPCAB was found to be associated with an attenuation of the stress response when compared with on-pump CABG surgery (33, 127). In contrast, in a comparison of on-pump CABG, OPCAB and thoracic surgery cases; Franke *et al.* (126) found an increase in pro-inflammatory markers, reaching a peak in 6 hours postsurgery in all groups. They found no difference between the OPCAB and on-pump CABG groups.

There is incompatibility between blood, human tissues and the synthetic material used in ECCs. Improvement of the ECC biocompatibility and management of the CPB circuit have been shown to reduce the magnitude of the inflammatory response (8, 49). Heparin-coated ECCs, aimed at improving haemocompatibility, reducing activation of plasma proteins and the inflammatory response, have also been investigated (49, 128). A study has shown an increase in thrombogenic resistance and a reduction in adhesion of plasma proteins with the use of biocompatible surfaces (129).

Other methods of myocardial protection, such as haemofiltration, have been described (128, 130). Ultrafiltration in particular, has been used more commonly in paediatric patients (131). During haemofiltration, blood is haemoconcentrated and some inflammatory mediators and excess body water in tissues is removed (128). The use of modified ultrafiltration and conventional ultrafiltration was compared with controls in one study (128). It was shown to reduce the increase in total body water to 4% with modified haemofiltration and to 15% with conventional haemofiltration; compared to 18% in the control group (128).

Visser *et al.* (130) in an RCT of 21 nondiabetic CABG patients, found that patients receiving a glucose-insulin-potassium infusion had significantly reduced levels of CABG-related SIRS markers, when compared with patients on tight glycaemic control. Use of some of the anti-inflammatory agents, such as aprotinin and corticosteroids, is debatable due to their undesirable side effects (37). While hyperthermia is known for its deleterious effects on organ function, the potential organ protective effects of hypothermia are not without some adverse

effects (132). Moderate hypothermia has therefore been seen as neutral ground between these extremes of temperature (132).

A brief prolongation of CPB during the reperfusion period was shown to be cardioprotective when compared with early commencement of inotropic drugs (133). Modifications to administration of cardioplegia, such as: giving warm blood cardioplegia; adding an energy substrate; administering cardioplegia during the resting period; combining ante- and retrograde reperfusate; and adding free radical scavengers, have been shown to improve myocardial perfusion, protection and recovery (62, 133). In animal studies, the addition of esmolol in cardioplegia was shown to lead to complete myocardial protection during global myocardial ischaemia (44).

A confirmation of the benefits of modifying cardioplegia was seen in a CABG trial (60). They found blood cardioplegia, particularly at tepid temperatures, to be superior to crystalloid cardioplegia. They found preservation of left ventricular function in the early postoperative period when tepid cardioplegia was compared with cold and warm cardioplegia. High-pressure retrograde perfusion was found to lead to tissue oedema (60). Antioxidants, calcium-channel blockers and magnesium in cardioplegia and in the prime solution were shown to reduce the incidence of ventricular arrhythmias and enhance myocardial recovery (44, 60, 62, 134-136).

Control of blood pressure variations and prevention of systolic excursions were shown to be associated with a reduction in morbidity and mortality (49),130). The “Evaluation of Clevidipine In the Perioperative Treatment of Hypertension Assessing Safety Events” (ECLIPSE) trial (125); investigated the association between 30-day mortality and the area under the curve of systolic excursions. They found that systolic excursions, proportionate to systolic blood pressure outside of the range of 75 to 135 mmHg intraoperatively; and 85 to 145 mmHg pre- and postoperatively, were significantly associated with mortality in high-risk patients (125).

Different institutions adopt a set of strategies for proactive myocardial protection that are then used as the standard (127). In the setting of this current study; moderate hypothermia, and warm ante- and retrograde blood cardioplegia were used. Only those patients undergoing isolated multivessel CABG on CPB were enrolled. Routine haemofiltration was not used. Corticosteroids were also not used routinely.

2.1.5 Anaesthetic agents and cardiac protection

Propofol, with structural similarities to phenol-based free radical scavengers, has been found to attenuate free radical mediated lipid peroxidation and systemic inflammation in patients with impaired myocardial function (3, 49). Propofol acts in a similar mechanism to the endogenous antioxidant vitamin E to scavenge reactive oxygen species (49, 137). Morphine elicits immunomodulatory actions on lymphocytes, granulocytes and macrophages. There is also evidence of morphine's reduction of myocardial ischaemic size. Fentanyl has a diminished ability to attenuate the inflammatory response. Midazolam has little influence on the body's defence systems (3, 49, 138).

Ketamine provides haemodynamic stability by preserving cardiac output through central nervous system stimulation and prevention of catecholamine reuptake in neutrons. Ketamine attenuates the increase in IL-6, IL-8 and TNF-α and therefore reduces the pro-inflammatory arm of the stress response. This suppressive effect on the inflammatory cascade may confer organ protective benefits. After CABG on CPB, ketamine was found to attenuate neutrophil activation and decrease IL-6 levels when compared with a placebo (3, 36, 139, 140).

Midazolam and thiopentone were found to effect their anti-inflammatory activity through inhibition of neutrophil function in an in-vivo investigation (141). Midazolam was also shown to significantly inhibit "lipopolysaccharide-induced up-regulation of proinflammatory mediators and activation of mitogen-activated protein kinase" (142). Nuclear factor-$\kappa\beta$ transcriptional activity was also suppressed. An animal study by Bartosikova *et al.* showed improved postischaemic recovery in hearts of rats pretreated with midazolam 0.5mg/kg intraperitoneally (143).

Kato and Foex (3), in a review of studies in predominantly animals using volatile and intravenous anaesthetics, made the following observations:

- the cardioprotective effects conferred by halogenated agents were in concentrations similar to those used in clinical practice 0.5-2.0 mean alveolar concentration (MAC)
- of the opioid anaesthetics, only morphine concentrations used experimentally were achievable in clinical scenarios (3 mg/kg)
- neutrophil adhesion during reperfusion was inhibited by ketamine at clinically relevant doses
- propofol concentrations used in animal studies showing cardioprotection, were at doses 10 times more than the clinical range
- volatile anaesthetic agents conferred myocardial protection when compared with nonvolatile anaesthetic agents in patients undergoing CABG and OPCAB (74).

In a meta-analysis of 27 studies with 2979 patients included, Symons and Myles (144) looked at myocardial protection with volatile anaesthetic agents during CABG surgery. Their endpoints included myocardial ischaemia, myocardial infarction, mortality, cTnI concentrations, inotropic support, cardiac index and length of ICU and hospital stay.

Only 5 studies had reported on mortality, 12 on MI and 8 on myocardial ischaemia (144). No significant differences were found in respect of MI, myocardial ischaemia, mortality and length of ICU stay. However, those who received volatile agents had significantly lower Troponin I concentrations compared with those who did not. They also had 20% higher cardiac indices, lesser inotropic support requirements and shorter hospital stays. This study included trials from 1985 to 2005.

The cardioprotective properties of volatile anaesthetics have been attributed to preconditioning (145, 146). Sevoflurane is said to elicit changes in the mitochondrial proteins involved in energetic metabolism (145, 146). The positive results of myocardial

preconditioning are supported by meta-analyses of experimental animal studies by Kunst *et al.* (2) and Klein *et al.* (136).

Looking back to earlier studies (1966–2005), Yu and Beattie (147) analysed data from 32 studies with 2841 patients. They too did not find a significant reduction in mortality rate in the 10 studies that reported on it. They did, however, find a reduction in the rate of MI with sevoflurane and desflurane. Of concern was a finding of an increase in the rate of MI with enflurane that they found in a post hoc analysis. Sevoflurane and desflurane were also found to be associated with significant reductions in cTnI. It would seem from this meta-analysis that not all volatile agents are cardioprotective but that enflurane may in fact increase the rate of MI (147).

Propofol, midazolam and short-acting opioid analgesics were used in this current study to avoid use of confounding cardioprotective agents such as morphine and ketamine. A volatile-agent-free anaesthetic was given throughout the entire perioperative period for the same reasons. In a recent systematic review of the literature which was followed by a consensus-based voting process, volatile agents, amongst all anaesthetic agents were selected as contributing towards lower mortality in cardiac surgery (148). They reported on interventions with a statistically significant effect on mortality in the setting of cardiac surgery through a systematic Medline/PubMed search and contacts with experts, and it was voted on by clinicians worldwide.

2.1.6 Alpha-2 agonists and myocardial protection in cardiac surgery

The following studies investigated the effects of pre-dexmedetomidine α-2 agonists such as clonidine on myocardial protection.

Helbo-Hansen *et al.* (84), in 1986 examined forty patients undergoing CABG surgery in an observational study. Twenty of them received decremental doses of clonidine while the other 20 served as controls. They found that plasma adrenaline and noradrenaline levels were less than ⅓ of the control group in the clonidine group 90 minutes postoperatively. In 1993

Dorman *et al.* (149) reduced adrenaline and noradrenaline levels post sternotomy in the clonidine group, but patients experienced much lower systolic blood pressures and more patients needed pacing. Aortic cross-clamp (Aocx) time was coincidentally shorter in the group that received clonidine.

Abi Jaoude *et al.* (150) performed an RCT of 24 patients looking at haemodynamic effects of clonidine premedication, and found that it conferred an unstable haemodynamic status requiring higher doses of vasoactive agents. Myles *et al.* (151) also found that clonidine led to more hypotension and bradycardia, despite the improvement in some aspects of quality of life parameters.

In 1999 Loick *et al.* (68), in an RCT of 70 patients, compared intravenous clonidine with high thoracic epidural anaesthesia (TEA) and placebo. They assessed troponin as a marker of myocardial ischaemia. An assessment of laboratory parameters was made at baseline, 30 minutes, 12 and 24 hours postoperatively. An increase in troponin levels was present in the first 24 hours in all groups, but less so in the clonidine than the control group. It was much higher than the TEA group. The only mortality in the study was in the clonidine group. Clonidine did not cause a significant attenuation of plasma epinephrine release. It was found to lead to adverse haemodynamic events (60, 116).

Clonidine is an α-2 adrenergic agonist that was investigated for cardioprotective properties before the advent of dexmedetomidine. The results of the effects of clonidine show inconclusive evidence towards cardioprotection.

2.1.7 Dexmedetomidine

Dexmedetomidine is a pharmacologically active S-enantiomer of medetomidine with a high affinity for α-2 adrenoreceptors at an α-2:α-1 ratio of 1600:1.21 (49, 82). It has a molecular weight of 236.7 Dalton, and is chemically described as (+)–4–(S)–1H–imidazole monohydrochloride (82, 83).

Dexmedetomidine has a rapid distribution phase (152). Its distribution half-life (t½) is 6 minutes; elimination half-life is 2 hours; and steady-state volume of distribution following intravenous administration is ±118 L (152). It exhibits linear pharmacokinetics in the dosage range of 0.2 to 0.7 μg/kg/hr as an intravenous infusion for up to 24 hours (146–148). Its clearance is estimated to be approximately 39 L/h for a 70-kg man (152-154).

It is produced as a white powder that is water soluble with a pKa of 7.1. It mixes with water to form a clear, colourless, isotonic solution with a pH of 4.5 to 7.0 (152-154). Its partition coefficient in octanol:water at pH 7.4 is 2.89 (152-154). Each millilitre contains 4 μg of dexmedetomidine hydrochloride (152). The solution is free from preservatives, additives and chemical stabilizers (152). Dexmedetomidine is a hypnotic-anxiolytic with a potential for up to 90% reduction in anaesthetic dose of isoflurane and halothane at higher doses (49, 152, 155, 156).

Dexmedetomidine has the ability to prevent changes in cardiac contractility, ejection fraction, stroke volume and calculated systemic vascular resistance (49, 124, 156). At doses, lower than 0.4 μg/kg/hr, it has been shown to have minimal haemodynamic adverse effects (124). It is proven to reduce the release of endogenous epinephrine and norepinephrine levels perioperatively (124, 156). In a study of 80 CABG patients, Jalonen *et al.* (76) found a 90% decrease in plasma concentrations of norepinephrine in patients who received dexmedetomidine.

“Existing data on dexmedetomidine in CABG surgery was said to be fragmented and derived largely from non-cardiac surgical patients, as well as patients in the ICU setting. This made it difficult to extrapolate results to CABG surgical patients” (35). Venn *et al.* (157), in a postoperative ICU study, showed dexmedetomidine to reduce IL-6 and attenuate the haemodynamic response to intubation in cardiac patients.

2.1.8 Dexmedetomidine and myocardial protection

2.1.8.1 Dexmedetomidine and myocardial protection in animal studies

A look at preclinical studies with dexmedetomidine and ischaemia-reperfusion introduces us to the cellular effects that inform the clinical trials that followed. These studies have either looked at induced regional or global ischaemia in animal models. The following studies experimented with varying periods of complete cessation of perfusion, mostly not exceeding 30 minutes, and found the following:

Flacke *et al.* (158), in anaesthetised dogs (1993) with induced global ischaemia, reported a decrease in central sympathetic outflow with decreased plasma catecholamines. A decrease in sympathetic and an increase in parasympathetic tone occurred. This resulted in a decrease in cardiac output per index, heart rate, and an increase in left ventricular end-diastolic pressure (LVEDP). Systemic vascular resistance index (SVRI) increased, and the rate of rise of left ventricular pressure (dP/dt_{max}) declined initially, and then stabilised. Systemic and transcoronary oxygen extraction increased, reflected by decreased mixed venous oxygen saturation at similar arterial oxygen content. There was vasoconstriction of the resistance, and not of the conductance coronary vasculature due to stimulation of cardiac sympathetic nerves.

In 2007 Okada *et al.* (159) looked at the effects of dexmedetomidine on global ischaemia-reperfusion. Five groups of isolated hearts were compared. Dexmedetomidine doses equivalent to doses used in ICU and translating to 0.23 ng/ml (dexmedetomidine 1) and 2.3 ng/ml (dexmedetomidine 10) were used. Dexmedetomidine 1 and dexmedetomidine 10 were compared with a dexmedetomidine-yohimbine mixture, yohimbine and control. Coronary blood flow was reduced in the dexmedetomidine groups. Preischaemic dexmedetomidine administration reduced infarct size, more significantly with the higher dose (dexmedetomidine 10) than lower (dexmedetomidine 1). This phenomenon was postulated to be due to the ischaemia preconditioning effect.

In 2010 Mimuro *et al.* (160) experimented with a global ischaemia model administering dexmedetomidine postischaemia. Dexmedetomidine worsened the infarct size compared with control. This study is highly important as it shows adverse outcome in administering

dexmedetomidine postischaemia. How this study translates to human studies is yet to be described.

Regional ischaemia studies, performed with occlusion of either the left main coronary artery or the left anterior descending artery (LAD), brought to light the very interesting physiological effect of dexmedetomidine at vascular level. This effect laid a foundation for clinical trials as follows:

Roekaerts *et al.* (161) also studied dog hearts and reported on this in 1996. They induced regional ischaemia and found similar haemodynamic results in a serial occlusion of the LAD with subsequent dexmedetomidine administration compared with placebo. Dexmedetomidine was seen to preserve blood flow in the mid- and endocardial compared with epicardial layers of the myocardial, in the face of coronary artery stenosis or ischaemia, resembling a "reverse steal" phenomenon. A slower heart rate favoured endocardial perfusion. There was an increase in endo/epicardial blood flow ratio in the postischaemic hyperaemic myocardium.

Kocoglu (162) and colleagues included 21 rats (2008) in their study and compared dexmedetomidine with coronary artery occlusion induced ischaemic episodes (IPC) and placebo on a regional ischaemia model. The infarct area was found to be smaller in the dexmedetomidine than in the IPC and control groups. The incidence of arrhythmias, however, was higher in the dexmedetomidine group.

In a study by Ibacache *et al.* (163) in 2012, rats' myocardium was exposed to a 30-minute regional ischaemia period with 120 minutes of reperfusion. A 25-minute period of dexmedetomidine preconditioning stimulated prosurvival kinases, reduced myocardial infarct size, and improved recovery.

The results of these preclinical studies point to the following:

- myocardial protection was achieved with controlled short-period (< 30 minutes) preischaemic administration of dexmedetomidine similar in effect to IPC

- a worsened effect was seen with postischaemia administration of dexmedetomidine
- post dexmedetomidine administration led to myocardial hyperaemia
- dexmedetomidine increased the risk of arrhythmias
- dexmedetomidine administration lead to vasoconstriction of epicardial coronary vessels
- dexmedetomidine also increased myocardial oxygen extraction.

2.1.8.2 Dexmedetomidine and myocardial protection in vascular patients

Patients presenting for vascular procedures have risk factors for coronary artery disease, with some already experiencing silent or symptomatic ischaemic heart disease. It is with this in mind that it became important to look at these patients' outcomes, as they mirror those presenting for CABG, albeit without the increased risk presented by CPB and direct myocardial injury from atriotomy.

Most of the work relating to this was done by Talke and coworkers (164) in San Francisco. They performed two studies with a cohort of patients that were at high risk of CAD. Their first report in 1995 presented a pilot study of 25 patients using 3 different doses of dexmedetomidine and placebo. They continued an infusion of dexmedetomidine up to 48 hours postoperatively. Importantly, patients were not allowed to mobilise while on the study drug in that 48-hour period. Cardiac enzymes were measured before surgery, and at 12 and at 72 hours postoperatively. Apart from better haemodynamic parameters within the dexmedetomidine groups, no discernible trend differences were recorded when compared with placebo. No evidence of major adverse cardiac events postoperatively could differentiate between the groups.

Their next study with a similar group of patients was reported in 2000 (165). In that study, 41 patients undergoing major vascular surgery were enrolled. A similar drug regimen was instituted with temporal decrements to the dexmedetomidine dose continuing until 48 hours in the postoperative period. One case of mortality occurred in the placebo group 7 weeks

postoperatively from multiorgan failure. Dexmedetomidine lowered plasma noradrenaline significantly at extubation in the treatment group compared with the placebo groups ($p < 0.05$). Adrenaline was significantly lower on postoperative day 1 in the treatment group ($p < 0.05$). No differences in the rate of adverse events were found.

It is worthwhile noting that the practice used by Talke *et al.* (164, 165) in both studies, whereby patients were kept immobile without any valid clinical reason for 48 hours postsurgery while the drug was being administered, is unfamiliar to anaesthesiology. This particular practice could introduce new problems such as respiratory infections and deep vein thrombosis due to immobility. It is therefore difficult to interpret and extrapolate Talke *et al.*'s studies in the context of CABG patients, particularly in the era of fast-tracking (extubation of cardiac patients within the first six hours postoperatively).

Biccard *et al.* (10) showed that, when compared with placebo, dexmedetomidine did not confer better all-cause mortality outcomes (point estimate 0.27, 95% CI 0.01–7.17, $p = 0.44$). The confidence interval for this result, although the OR is below 1, is wide and includes the null value. It is therefore likely to be imprecise, due to the small sample size.

2.1.8.3 Dexmedetomidine and catecholamines in CABG surgery

The neurohumoral response elicited by CPB includes a cascade that involves catecholamines. A literature review on the effects of dexmedetomidine on catecholamines is necessary as this could account for some of the effects of dexmedetomidine. The first citable human study was by Jalonen *et al.* (99) in Finland, conducted as a randomised, placebo-controlled and double-blind, parallel group design study of 80 patients, enrolled between June 1992 and March 1993. Forty patients were allocated to each branch of the study. The inclusion criteria were: good left ventricular function; age younger than 70 years; and weight less than 100 kg. All patients with severe concomitant systemic diseases were excluded. Patients with left main CAD with stenosis of more than 50% were also excluded.

Their primary outcomes were the determination of plasma adrenaline and noradrenaline from baseline, 5 minutes after tracheal intubation, 1 minute after sternotomy, before aortic unclamping, immediately post CPB, 1 and 2 hours postoperatively, and on the first postoperative morning. They found that there was no statistically significant difference in the mean of adrenaline levels between the groups ($p = 0.250$), but there were statistically significant differences in the increase in noradrenaline between groups at the end of surgery and 2 hours postsurgery ($p < 0.001$) (99).

In China Ren *et al.* (166) enrolled 160 patients presenting for OPCAB between January 2010 and January 2011. Patients were randomised into dexmedetomidine and placebo groups. They presented for three to four vessel lesion CABG surgery. Their preoperative cTnI levels were within normal limits. Patients older than 75 years, ejection fraction (EF) < 40%, and arrhythmias preoperatively, were excluded. Diabetes and obesity, which are linked to ongoing systemic inflammatory disease, were also excluded.

Levels of noradrenaline immediately, and 12 hours postsurgery, were significantly lower in the dexmedetomidine than the control group ($p < 0.05$). Catecholamine levels in the dexmedetomidine group reverted back to be equivalent to the control group (after 48 hours)**.**

There is therefore unequivocal evidence from animal and human studies that dexmedetomidine attenuates the increase in levels of noradrenaline but not adrenaline when compared with placebo.

2.1.8.4 Dexmedetomidine and inflammatory markers in CABG surgery

Inflammation is a significant contributor to perioperative morbidity. Preclinical studies by Lai *et al.* (167) and Taniguchi *et al.* (168) showed that early administration of dexmedetomidine attenuated the increase in cytokine release.

A meta-analysis of the effects of dexmedetomidine on inflammatory markers by Li *et al.* (169) reported significant decreases of IL-6, IL-8 and TNF-α immediately after surgery and on the 1st postoperative day. IL-10 was significantly increased on day 1 after surgery. This study included patients that underwent any type of surgical procedure or traumatic intervention. Bulow's group (106), in their investigation of patients undergoing CABG with mini-CPB, found a significant proportionally higher increase in IL-1 and IL-6 in the total intravenous anaesthesia (TIVA) group compared with the TIVA-dexmedetomidine group ($p < 0.0001$), but found no difference in the decrease in IL-10.

In Chen, *et al.*'s study (170), a group of CABG surgery cases with CPB was investigated and it was found that the up-regulation of pro-inflammatory (TNF-α, IL-6 and IL-8) markers was significantly attenuated by the addition of dexmedetomidine. IL-10, an anti-inflammatory cytokine, was up-regulated in the dexmedetomidine group compared with the control group ($p < 0.05$). Ren *et al.* (166) instead looked at cortisol levels at 12 and 24 hours post-CABG and found lower levels in the dexmedetomidine group compared with the control group, but similar levels at 48 hours and beyond. In a study by Ueki *et al.* (171), an RCT of 42 patients also found that dexmedetomidine attenuated the increase in IL-6 from 1 hour post-CPB to postoperative day 3 ($p < 0.05$).

On the contrary, Farsad *et al.* (172) found an increase in TNF-α in their dexmedetomidine group compared with placebo. They performed an RCT with 61 patients, randomised to dexmedetomidine and placebo. They also found no difference in outcome in IL-6, and IL-10 levels.

This review therefore concludes that there is some evidence that dexmedetomidine attenuates the rate of increase in pro-inflammatory markers and promotes the increase in anti-inflammatory marker, IL-10. The evidence is, however, conflicting (106, 169, 172).

2.1.8.5 Dexmedetomidine and ischaemic markers in CABG surgery

Aspects of the patients' profiles and different anaesthetic and surgical methods have a potential to influence the outcome in CABG surgery, as evidenced by previous studies (120, 144, 146, 147, 173-175).

The current study sought to investigate the effects of dexmedetomidine on **high-sensitivity troponin (hs-cTn) when compared to placebo in CABG surgery**. A systematic search of the literature using the population, intervention, comparison and outcome (PICO) model of researchable questions was used to review the literature addressing this. The following databases were searched: Scopus, Cochrane Library, PubMed Central, ProQuest and Web of Science. The medical subject headings (MeSH) used were: "dexmedetomidine" AND "high-sensitivity troponin" OR "hs-cTn" OR "high-sensitivity cTn" AND "coronary artery bypass graft" OR "CABG" AND "surgery". The following limits were applied: "human", "age>19years", "randomised controlled trials" and "01 January 2008 to 30 April 2018".

The search identified 43 studies (PubMed – 0, ProQuest – 0, Web Of Science – 26, Cochrane Library – 4, and Scopus – 13). Abstracts from thirteen studies were screened by two reviewers independently. **No studies were identified reporting on the effects of dexmedetomidine on hs-cTn (high-sensitivity troponin) compared to placebo/other therapy in CABG surgery**. Previous studies on the effects of dexmedetomidine compared to other therapies (or placebo) in cardiac surgery reported outcomes with conventional (non high-sensitivity) troponin (cTnT and cTnI). Literature on the effects of dexmedetomidine on cTn (non high-sensitivity troponin) during CABG surgery on and off cardiopulmonary bypass was found instead and is therefore reviewed as follows:

In Shandong, China, Ren *et al.* (176) conducted a prospective randomised, unblinded study of 160 patients presenting for OPCAB between January 2010 and January 2011. Patients presented with three to four vessel coronary lesions. Preoperative cTnI levels were within normal limits. Their exclusion criteria were: age < 75 years, EF < 40%, preoperative arrhythmias, diabetes mellitus and obesity. Propofol was given at induction and as an infusion

intraoperatively. Following the first vascular anastomosis, continuous infusion of dexmedetomidine 0.2–0.5 μg/kg/h was given until 12 hours postarrival in ICU.

Blood samples for cTnI and CKMB were collected at induction, immediately postsurgery and at 12, 24, 48 and 72 hours postsurgery. Demographics and surgical characteristics were similar in both groups. The difference in cTnI and CKMB levels immediately and 12 hours postsurgery was statistically significant ($p < 0.05$) between groups. However, there was no difference in cTnI levels at 24, 48 and 72 hours between groups. Since theirs were OPCAB surgery patients, it is important to note that they did not experience a period of ischaemia-reperfusion, and therefore their level of inflammatory response is known to be lower than that in CPB patients (120).

In China (Hubei), Chi *et al.* (177) prospectively recruited patients between June 2012 and December 2013 in a randomised, double-blind, parallel group trial. Morphine was given as premedication and a sufentanil-sevoflurane anaesthetic as maintenance. Patients presenting for OPCAB surgery (n = 105) were subsequently recruited, and 5 patients were excluded from the final analysis as they crossed over from OPCAB to CABG on CPB. Two different doses of dexmedetomidine were given; high dose: 1 μg/kg loading and 0.6 μg/kg/hr maintenance and low dose: 0.6 μg/kg loading and 0.3 μg/kg/hr maintenance, and control group. Serum cTnI and CKMB samples were taken before surgery, and 24 and 48 hours postsurgery.

No difference between the low-dose dexmedetomidine and control groups was seen at 24 and 48 hours in relation to cTnI ($p = 0.675$ and $p = 0.549$) and CKMB ($p = 0.128$ and $p = 0.402$), respectively. No significant difference in cTnI levels was seen at 24 hours between groups ($p = 0.097$). A significant difference in 48 hours postsurgery was seen between the high-dose dexmedetomidine and ($p < 0.001$) and the control group. Although Chi *et al.* (177) labelled this dose as a "high" dose, the dose that they used was one used in clinical practice as a recommended dose (0.6 μg/kg/hr). The results with the "high" anaesthetic dose of dexmedetomidine differed from those seen in Ren *et al.* (176), who found a statistically significant difference immediately and 12 hours postoperatively.

Kim *et al.* (178) in Seoul, Korea, in 2014, randomised 160 patients, but analysed 153. The patients had undergone OPCAB surgery and were subdivided into four groups; lignocaine, lignocaine-dexmedetomidine (Lido-DEX), dexmedetomidine (0.3–0.7 μg/kg/hr) and control groups. Lignocaine, and not dexmedetomidine, was found to reduce postoperative ischaemic markers. The reduction in cTnI in the Lido-DEX group, when compared with control, was statistically significantly on day 2 (48 hours postoperatively): cTnI 0.74(0.39–1.37) ng/ml vs. 0.63(0.35–1.64) ng/ml vs. 1.07(0.65–2.48) ng/ml in the lignocaine, Lido-DEX and control groups, respectively. They found the difference in ischaemic markers in the lignocaine group compared with control, and Lido-DEX compared to control to be statistically significant, ($p = 0.003$ and $p = 0.048$ respectively).

Similarly, CKMB on day 1 in the three groups were 7.67 (5.78–11.92), 7.18 (5.01–11.72), and 13.19 (6.85–23.87) in the lignocaine, Lido-DEX and control groups respectively. The differences between the lignocaine vs. control and Lido-DEX vs. control groups was statistically significant, ($p = 0.003$ and $p = 0.015$ respectively). CKMB on day 2 was 3.01 (1.44–4.39), 2.83 (1.57–4.09), and 4.84 (2.63–10.68) in the lignocaine, Lido-DEX and control groups respectively, with significant differences in the lignocaine vs. control ($p = 0.001$), and Lido-DEX vs. control groups ($p = 0.001$). Lignocaine is intensely cardioprotective. These results are consistent with the findings by Chi *et al.* (177) and seem to suggest that, on its own, dexmedetomidine is unable to attenuate the rise in ischaemic markers (179).

Between 2011 and 2012 in Santa Maria, Brazil, Bulow *et al.* (106) enrolled 30 patients undergoing CABG with mini-CPB, for a depth of anaesthesia monitored propofol and sufentanil total intravenous anaesthesia (TIVA) vs TIVA-dexmedetomidine study. Patients were randomly assigned to TIVA ($n = 15$) and TIVA-dexmedetomidine group ($n = 15$). Low dose dexmedetomidine of 0.3 μg/kg/hr was given. Blood samples were collected as follows: baseline, 90 minutes, 5 hours and 24 hours after starting mini-bypass.

They measured CRP, CK, CKMB, cTnI and cortisol. No difference in increases of enzymes with a dose of 0.3 μg/kg/min dexmedetomidine was seen according to the authors. It is

important to note, as illustrated in previous studies, that mini-CPB does not elicit a neuro-humoral response similar to conventional CPB (102, 120, 175). The observation therefore was that, a set low dose of dexmedetomidine on mini-CPB, not adjusted to anaesthetic needs, did not confer cardioprotection.

In Turkey Tosun *et al.* (180) randomised 38 patients between the ages of 39 and 80 years undergoing elective CABG with conventional CPB to dexmedetomidine (n = 18) and placebo (n = 20). Dexmedetomidine was given as a loading dose followed by an infusion in a moderate dose of 0.5 μg/kg/hr continuously up to the end of surgery. Fentanyl-sevoflurane anaesthesia was used. Methylprednisone 30 mg/kg was administered on both arms of the study. They excluded patients with redo surgery, valve surgery, unstable angina, elevated ischemic enzymes, use of a balloon pump and EF ≤ 40%.

Cardiac markers increased significantly post CPB in both groups. However, there were no differences in CKMB, cTnT and NT-proBNP values for all measurement intervals between dexmedetomidine and placebo at 24 hours post aortic declamping. Sevoflurane has been shown to confer preconditioning in cardiac patients (145). It was administered to both groups in addition to methylprednisone, an anti-inflammatory agent.

The mechanism of action of dexmedetomidine has been postulated to be through preconditioning, similar to volatile agents. The actions of the two agents together (sevoflurane and methylprednisone), on preconditioning and inflammation, may have rendered the effects of dexmedetomidine undetectable and negligible.

In Jiangxi, China, Chen *et al.* (170) enrolled 65 patients presenting for CABG with CPB between March 2013 and August 2014. They were randomised to receive either dexmedetomidine or saline. Blood samples were taken at baseline, 15 minutes, 2 hours and 24 hours after declamping. Anaesthesia was maintained with sufentanil, propofol and sevoflurane.

They found a 2-fold decrease in CKMB and cTnI enzymes in the dexmedetomidine group when compared with saline at 2 hours postsurgery. They also found a 1.6-fold decrease in CKMB and cTnI enzymes at 24 hours post cross-clamping, at a dose of 0.5 μg/kg/hr ($p < 0.01$). In this instance, propofol, a free radical scavenger was added to sevoflurane. Evidence of dexmedetomidine cardioprotection was seen in this study despite it being conducted in a similar manner to the study by Tosun *et al.* (180). The difference between the two studies was that Tosun's group (180) routinely administered a steroid in both groups in addition to sevoflurane. The results of these two studies, therefore, showed equivocal results.

In Prague Riha *et al.* (181) conducted a retrospective analysis among 38 patients aged younger than 75, with EF ≥ 45% and normal cTnI levels, who had CABG on CPB between January and September 2010. No steroids where given to any of the patients. Hs-cTnI and CKMB blood samples were taken on arrival in ICU and on the morning of the first postoperative day. They used racemic ketamine in combination with dexmedetomidine (KET-DEX) (dexmedetomidine 0.5–1.5 μg/kg/hr) and compared with anaesthetic doses of sufentanil and sevoflurane. They found no significant difference between the two groups in ischaemic biomarkers in the immediate postoperative period.

However, on the first postoperative morning, the KET-DEX group exhibited a statistically significant decrease in ischaemic biomarkers, cTnI ($p = 0.02$) and CKMB ($p = 0.01$). Sevoflurane, a preconditioning agent was being compared with two potentially cardioprotective agents. The two potentially cardioprotective agents in KET-DEX act through different mechanisms (139, 182) to each other and to sevoflurane.

The better outcome and the difference in biomarkers seen on the morning of the first postoperative period could be attributed to the long-acting nature and cardioprotective effects of ketamine and its metabolites; norketamine and dehydronor-ketamine (182). The elimination half-life of ketamine is 2 to 3 hours and the volume of distribution is 3 L/kg (182). Ketamine has been found to attenuate the inflammatory response (139, 183) and

troponin levels in cardiac surgery (184). Therefore, Riha's results are to be interpreted in this context.

Ji *et al.* (14), in a retrospective analysis of patients who had CABG surgery, compared dexmedetomidine to conventional anaesthesia. They concluded that dexmedetomidine attenuated the increase in ischemic and inflammatory markers. They also found favourable postoperative morbidity and mortality in the dexmedetomidine group (14). Their two groups, however, were not matched. There were statistically significant differences in both baseline and perioperative characteristics between the groups. The factors that were different are those that have been found to impact significantly on outcome in other studies, such as Aocx time, CPB time, EF and CCF (185-187).

The current study will therefore **investigate the effects of dexmedetomidine on hs-cTnT in CABG surgery using CPB**. This study will seek to determine the difference in changes in hs-cTnT between the dexmedetomidine and placebo groups during CABG surgery on CPB. The current study will also seek to investigate the effects of dexmedetomidine "unassisted" by other "cardioprotective" agents during cardiac surgery such as those presented in a recent updated consensus process (148).

Most studies reviewed in the literature and reported in this literature review with data on the effects of dexmedetomidine on cTn changes in cardiac surgery were predominantly underpowered to make conclusive deductions. The power estimation for the current study was performed using means from cTn studies. A post-hoc power calculation will be performed to determine the estimated optimal sample size for a power of 80% with an α angle of 0.05 given the difference in means that will be found. This will assist in informing future research planning and methodology. A systematic review of **the effects of dexmedetomidine on changes in cTn in cardiac surgery** will also be undertaken as part of this thesis in chapter 9.

2.1.8.6 Dexmedetomidine, length of stay in hospital/ICU and mortality in CABG surgery

In the retrospective study by Ji *et al.* (14), 724 patients were enrolled from a single hospital database. They looked at the effects of dexmedetomidine on the following: in-hospital, 30-day and 1-year all-cause mortality; 30-day readmission; and length of hospital and ICU stay. Their results showed an association between dexmedetomidine and a significant reduction in "in-hospital, 30-day and 1-year mortality rates of 1.5% and 4.0% (adjusted OR = 0.332, 95% CI 0.155–0.708; p = 0.0044), 2.0% and 4.5% (adjusted OR = 0.487, 95% CI 0.253–0.985; p = 0.0305) 3.2% and 6.9% (adjusted OR = 0.421, 95% CI 0.247–0.718; p = 0.0015) respectively".

They used propensity score matching for their heterogeneous groups. There were statistically significant differences in baseline characteristics (dyslipidaemia, CCF, EF, preoperative MI, renal failure and family history of MI) and procedural characteristics (perfusion time, aortic cross-clamp time and use of intraaortic pump) ($p < 0.05$) in this study. These factors on their own were found to be associated with adverse outcomes in previous studies (186, 187).

An analysis of length of stay in hospital and in ICU by Chi *et al.* (177) showed a significant increase in hours in ICU in their "high"-dose dexmedetomidine group compared with control mean (SD) 53.1(10.4) hours vs. 41.9(6.0), $p < 0.01$, high dose and control, respectively, and no difference in LOS in hospital days mean(SD) 15.6(2.3) vs.15.3(2.0) vs. 16.4(2.0), p = 0.10, high dose, low dose and control, respectively (177). No differences were found when a lower dose of dexmedetomidine was used. Since their "high"-dose dexmedetomidine was 0.6 μg/kg/hr, a normal recommended anaesthetic/sedation range, it meant that using the normal recommended dose led to an increase in ICU LOS. In a group of patients older than 65 years, Cheng *et al.* (188) found a significant increase in intubation time and LOS in ICU in the dexmedetomidine group.

Kim *et al.* (178) investigated the effects of lignocaine-dexmedetomidine versus control on postoperative length of hospital stay, complications and 1-year mortality rates. They found no differences, despite significant differences in enzyme concentrations between the lignocaine-

dexmedetomidine and control groups. Postoperative ICU and hospital stay, and 1-year mortality between the lignocaine-dexmedetomidine and control groups were 2(2–3) vs. 2(2–3) days (p = 0.064), 10(8–13) vs. 10(6–11) days, (p = 0.06), 0 vs. 1(3%) (p = 0.363), respectively.

In a prospective study of 30 participants by Bulow *et al.* (106), between the group that received dexmedetomidine and TIVA-dexmedetomidine, there were no differences in length of stay in ICU and hospitalisation, (4±1 vs 4±1 and 7±1 vs 8±2) days respectively (106).

Tosun *et al.* (180) also showed no difference in length of ICU stay between the placebo and dexmedetomidine groups in an RCT, 83.05(15.86) vs. 67.23(8.10) days, p = 0.36. Similar results were also reported by Riha *et al.* (181) in their retrospective study with length of stay in ICU 22.8 (21.8–23.2) hr vs. 23.5 (18.2–25.9) hr, in their sevoflurane-sufentanil and ketamine-dexmedetomidine comparison, respectively. Their 30-day mortality results were also similar between these two groups.

In Table 2.1 is a list of studies that investigated dexmedetomidine in CABG surgery with anaesthetic methods, surgical approach, the addition of cardioprotective agents and 24-hour troponin outcomes (sources included).

Table 2.1: Randomised controlled studies of dexmedetomidine in CABG surgery

Author (Ref)	cTn 24-hours	Other cardioprotective agents	Study type	Surgical type	cTn type	Subjects number (n)
Bulow *et al.* (106)	–	Nil	Randomised	Mini-CPB	cTnI	30
Chi *et al.* (177)	–	Sevoflurane, morphine	Randomised	OPCAB	cTnI	100
Chen *et al.* (170)	+	Sevoflurane	Randomised	CPB	cTnI	65
Kim *et al.* (178)	–	Lignocaine	Randomised	OPCAB	cTnI	153
Ren *et al.* (176)	–	Nil	Randomised	OPCAB	cTnI	160
Tosun *et al.* (180)	–	Methylprednisone	Randomised	CPB	cTnT	38

Dexmedetomidine compared to placebo with or without other cardioprotective drugs and results on ischaemic marker troponin at 24 hours; CPB – cardiopulmonary bypass; OPCAB – off pump coronary artery bypass

2.1.9 Summary of the literature regarding the impact of dexmedetomidine in CABG surgery

- In preclinical studies, dexmedetomidine was administered for a maximum of 30 minutes, with subsequent reperfusion of the myocardium (160, 189, 190).
- In clinical studies, the administration of dexmedetomidine differs, the time periods of blood sampling differ, and the results differ at different time periods (166, 170, 178, 180).
- While the evidence of reduction of plasma noradrenaline seems consistent, there is conflicting evidence regarding the reduction of plasma adrenaline in CABG surgical patients who received dexmedetomidine (99, 166).
- Animal studies seem consistent in showing attenuation of inflammatory markers with dexmedetomidine administration (167, 168).

- There is inconclusive evidence of attenuation of pro-inflammatory markers when dexmedetomidine was compared with controls in clinical studies in cardiac surgery (169).
- There is inconclusive evidence regarding the impact of dexmedetomidine on IL-10 (170, 172).
- Evidence from randomised, controlled trials suggest that there were no differences in perioperative outcomes such as mortality, and hospitalisation (177, 178, 180).
- There was inconclusive evidence on length of ICU stay (11, 178, 191, 192)
- Use of additional anti-inflammatory and cardioprotective agents seem to confound the effects of dexmedetomidine (178, 180).
- Due to the differences in outcome attributable to different surgical strategies, these have also contributed to differences in outcome (106, 178, 180).
- Different doses and infusion protocols affected outcome, as seen in both preclinical and clinical studies (159, 177).

2.2 Dexmedetomidine, biomarkers and prediction of outcome

In a linear, multivariate regression analysis of total cost, LOS in ICU and LOS in hospital, Patanwala and Erstad (193), in a multivariate regression analysis, found an association between use of dexmedetomidine and increased length of ICU stay (coefficient 0.70, 95% CI 0.59–0.81, $p < 0.001$), and overall length of hospital stay (coefficient 0.55, 95% CI 0.45–0.65, $p < 0.001$). They also found an association between use of dexmedetomidine and increased hospital costs (coefficient 0.56, 95% CI 0.46–0.65, $p < 0.001$).

A multivariate analysis by Kangasniemi *et al.* (194) looking at 1098 patients undergoing CABG surgery, showed that CRP level was an independent predictor of all-cause mortality (RR 1.60, 95% CI 1.09–2.35, $p = 0.017$) in patients with a left ventricular ejection fraction below 50%. Their analysis included factors that affect outcome such as recent MI, CCF, age and diabetes mellitus.

Young *et al.* (195) undertook a meta-analysis to determine the predictive value of proBNP towards postoperative cardiac complications. They included 24 studies with 5438 patients. They found that proBNP was predictive of adverse outcome (OR 13.9, 95% CI 8.43–23.8), with postoperative proBNP levels more predictive than preoperative levels.

Hs-cTn has long been suggested as a predictor of outcome (114, 196-198). In their study of 37 patients, Kocak *et al.* (196) suggested that hs-cTnT may be more predictive of ischaemia than conventional cTnT. They found better correlation between myocardial injury and hs-cTnT ($r = 0.719$, $p < 0.001$) compared with cTnI ($r = 0.544$, $p < 0.001$). On the other hand, Petaja *et al*. (197) used cut-off values of 14 ng/L and 500 ng/L for preoperative and postoperative hs-cTnT measurements respectively. They found that the addition of Euro-score II increased the association with 180-day mortality. Lurati Buse *e*t *al.* (127) in a meta-analysis suggested that the association between troponin levels and outcome are affected by population type, cTn subtype, cTn assay and sampling time (121).

Using a regression model, Eigel *et al.* (198) looked at 540 patients and found cTnI at the end of CPB, age, gender and CPB time to be significantly associated with adverse outcome. Fellahi *et al* (114) found a 2-year postoperative mortality from cardiac causes and non-fatal cardiac events to be significantly associated with high cTnI levels.

Our study was undertaken to investigate the effects of dexmedetomidine in CABG surgery with CPB in the absence of other proven cardioprotective and anti-inflammatory agents when compared with placebo (Table 2.1). The sampling time was 24 hours post induction of anaesthesia. We specifically looked at the impact of dexmedetomidine on biomarkers such as NT-proBNP, hs-cTnT and CRP, as well as clinical outcome measures such as LOS in ICU, LOS in hospital and 30-day mortality.

2.3 Ethnicity and CAD, dexmedetomidine and pharmacoethnicity

2.3.1 Ethnicity and CAD

The previous chapter reviewed international literature, and work previously done in South Africa and sub-Saharan African countries with regards to the influence of ethnicity on CAD, its risk factors and the pharmacodynamics of dexmedetomidine.

A track of the trends in CAD and associated risk factors in Sub-Saharan Africans by Okinboboye *et al.* (24) shows a steady increase in prevalence of the disease, reported in the middle of the 20th century by authors from Tanzania, South Africa and Nigeria. The Prospective Urban Rural Epidemiology (PURE) study (199) including the Sub-Saharan African region, a survey of adults examining the relationship of societal influences on: human lifestyle behaviours; cardiovascular risk factors; and incidence of chronic non-communicable diseases(199). One interesting finding of this study is that "total fat and types of fat were not associated with cardiovascular disease, myocardial infarction, or cardiovascular disease mortality, whereas saturated fat had an inverse association with stroke" (200)

Studies performed in South Africa before 1994 show a very low prevalence rate of coronary artery disease among Africans (84-88). Due to the locations and the timing of these studies, the reported proportions of disease between different ethnic groups should be read in the context of the political dispensation at the time whereby public health services were not equitably distributed among the different population groups. This would therefore have affected where patients presented. An analysis by Schwartz *et al.* (88) of patients admitted to CHBAH (Soweto) between 1951 and 1961 found a prevalence of CAD disease rate of 0.01% in African patients.

Later, in 1970, Seftel *et al.* (201, 202) reported in the Johannesburg Hospital (Hillbrow), a prevalence of 0.6% in African patients whilst Schrire *et al.* (191) reported a rate of 1.4% in Cape Town's African patients at the same time. At King George Hospital (Durban) in 1986, a study by Seedat *et al.* (203) found the prevalence of CAD (elicited by questionnaire) to be 2.4% in African patients. Joubert *et al.* (87) looked at African stroke patients in Medunsa

(Pretoria) between 1984 to 1993 and found resting ECG evidence of myocardial ischaemia in 14.6% and MI in 5.8% of patients.

It is clear from these reports that by the early 1990s, the reported prevalence of CAD in the African population appeared to be on the increase. In a retrospective Baragwanath hospital cohort of 500 consecutive patients who presented for diagnostic coronary angiography between January 1998 and December 1999; 41% of the patients with significant CAD were African patients (26). No significant differences between African and non-African patients were found with regard to baseline coronary risk factors. This study at Baragwanath hospital (26), may have shown a skewed reflection of prevalence of disease, as a large proportion of patients who would present to this hospital are African.

Steyn *et al.* (89), in a 2005 study of risk factors associated with MI in Africa, as a part of the INTERHEART Africa study, recruited participants from 9 countries. More than 80% of these were from South Africa. Thirty-six per cent of them were African patients (144 cases and 352 controls). The prevalence of smoking (on history), diabetes mellitus, hypertension, abdominal obesity and cholesterol was higher in the INTERHEART group than in controls (89). The study showed an epidemiological transition in Africans similar to that seen in African Americans (89).

Tibazarwa *et al.* (91, 204) reported an increased incidence of CVD risk factors in participants, in their Heart of Soweto Study's Heart Awareness Day. Obesity was found to be the most prevalent risk factor overall (43%), with women presenting as more obese than men (55% and 23%). This was followed by high blood pressure and elevated total nonfasting cholesterol levels (204). This study also compared a skewed population group. This current study, explores the influence of ethnicity and gender in the prevalence of CAD and risk factor profile in patients presenting for CABG surgery at a tertiary hospital.

In exploring ethnicity and risk factors and their influence on prevalence of CAD, Seedat *et al.* (205) found a high prevalence of hypertension (25%) in urban Zulus compared with 17.2%

and 14% in whites and Indians, respectively. However, this did not translate into a higher prevalence of CAD in these Zulus. In 1994, Seedat *et al.* (203) found that smoking, hypercholesterolemia and hypertension were major risk factors in whites while they found hypertension, smoking and obesity to be important risk factors in female patients.

Isles *et al.* (206) also concluded that, although Africans in their study had a higher prevalence of hypertension, it was not commonly associated with CAD, but rather with cerebrovascular disease. There is a suggestion from the literature that although African patients have a high incidence of hypertension, they present more commonly with hypertensive heart disease, strokes and renal complications, but not with a high prevalence of CAD (207). There is a suggestion of high fibrinolytic activity that is postulated to contribute to lower CAD rates when compared with other ethnic groups (24, 208).

Ethnic and gender differences have been shown as a factor in the presentation of disease processes and risk factors in several other studies (89-92). Genetic variability, linked to ethnicity, is known to have a relationship with pharmacogenetics and pharmacogenomics (93-95). The variability expresses itself in the form of differences in drug metabolism, transport proteins and drug target sites (93). Dexmedetomidine, which acts on the α-2 adrenal receptor, has also been shown to be subject to these variabilities (96, 97).

2.3.2 Dexmedetomidine, pharmacoethnicity and cTn

The studies reviewed in the literature did not report on the influence of ethnicity on the effects of dexmedetomidine on troponin (cTnT and cTnI) levels in cardiac surgery. The literature was searched systematically using the population, intervention, comparison and outcome (PICO) model of researchable questions to identify studies that reported on this. The following databases were searched: Scopus, Cochrane Library, PubMed Central, ProQuest and Web of Science. The major medical subject heading (MeSH) terms used were: “dexmedetomidine” AND “Race” OR “ethnic groups” OR “Ethnicity” AND “troponin” OR “cTn” OR “cTnT” OR “cTnI” AND “cardiac” OR “heart” AND “surgery” AND “01 January 2008 to 30 April 2018”.

The search identified 140 studies (PubMed – 97, ProQuest – 3, Web Of Science – 24, Cochrane Library – 16, and Scopus – 0). **None of the studies considered the effects of dexmedetomidine on troponin changes associated with ethnicity in cardiac surgery. The titles and abstracts scanned suggested that these studies addressed the effects of dexmedetomidine on clinical outcomes associated with ethnicity instead.** These studies that reported on the effects of dexmedetomidine on clinical outcomes associated with ethnicity are discussed:

Holliday *et* al. (94) reviewed the literature on interpatient variability in clinical and sedation outcomes associated with dexmedetomidine. They described the genetic α-2 receptor polymorphism and interpatient variability in dexmedetomidine response with cardiovascular and sedation outcomes.

Dexmedetomidine was shown to display variable interpatient clinical responses in both healthy and ICU patients (96, 209). Metabolic and genetic (CYP2A6) variations were suggested as possible reasons for these variations (96). These variations had manifested in differing cardiovascular and sedation responses to dexmedetomidine (96, 209). The vascular effects of dexmedetomidine between ethnic groups showed a wide interpatient variability, however, ethnicity was not found to be related to these changes (209).

Kurnik *et al.* (210) found a substantial interindividual variability in the reduction of systolic blood pressure (range, 1 to 34 mm Hg) and plasma norepinephrine concentrations (range, 24 to 424 pg/mL). However, they did not find a significant difference between "black and white" subjects in their dexmedetomidine responses ($P>0.16$ for all outcomes), before or after adjustment for covariates. They also did not find a relationship between genotypes ADRA2C del322-325 and GNB3 C825T in response to dexmedetomidine (all $P>0.66$).

Conversely, Tellor *et al.* (211) found an association between non-African race and sedation intolerance in their ICU study (OR 9.5, 95%CI 1.16–77.91, $p = 0.03$). The differences in

response between the different ethnic groups were thought to be due to the link between genetics and ethnicity (94). Genetic α-2 receptor polymorphism has also been suggested as a reason for interpatient dexmedetomidine response (94).

Gene polymorphism showed a significant response on effects of sedation with dexmedetomidine (212). A common gene variant was found to be associated with a dexmedetomidine blood pressure response in one study (97). A previous study had shown ethnic differences in the blood pressure response to clonidine administration (213). Clonidine, however, has effects on both α-1 and α-2 receptors, which may have had an influence on the results. This type of ethnic difference in blood pressure response was not found with dexmedetomidine (209).

Kohli *et al*. (96) explored the effects of differing metabolic rates in response to dexmedetomidine in patients with identical alpha adrenergic genotypes. They divided these patients into different metaboliser groups. They found no significant differences between the different metaboliser groups. They also found no significant association with a specific genotype. Previous studies had found no association with age, smoking, gender or body weight in response to clonidine (214) and dexmedetomidine (215).

This current study will investigate the effects of dexmedetomidine on hs-cTnT, other biomarkers and clinical outcomes related to ethnicity as a subgroup analysis.

CHAPTER 3 : RESEARCH METHODOLOGY

3.1 Hypothesis

1. In patients undergoing CABG surgery with total intravenous anaesthesia, in the absence of any other proven cardioprotective anaesthetic agent, dexmedetomidine protects the myocardium from ischemia-reperfusion injury, as evidenced by:

- attenuation of increase in ischaemic marker (hs-cTnT)
- down-regulation of inflammatory biomarker IL-6 and up-regulation of IL-10
- a decrease in ICU stay and hospitalisation
- a reduced 30-day mortality compared with placebo.

2. Preoperative plasma inflammatory marker CRP and cardiac biomarkers NT-proBNP and hs-cTnT are predictive of short-term outcome in patients undergoing CABG surgery.

3. The prevalence of coronary artery disease in African patients presenting for CABG is lower than other ethnic groups.

3.2 Methods

3.2.1 Study design

A prospective double-blind, randomised, placebo-controlled trial was undertaken (Flow Diagram 4.1). Randomisation was performed by an independent pharmacist who was the only person not blinded to the study. A list from 1 to 90 was prepared before the study commenced. Forty-five dexmedetomidine and 45 placebo entries were randomly assigned. As patients were enrolled, the pharmacist allocated them into consecutive numbers and prescribed and prepared the blinded randomly assigned drug. Both the patient and the anaesthesiologist were blinded to what was given. The “drug” in the sterile syringe, prepared by the pharmacist at commencement of the procedure, was treated as though it was dexmedetomidine. Infusion rates of 3–7 μg/kg/hr were titrated to the “needs” of the patient in conjunction with other intravenous anaesthetic agents given. A standardised anaesthetic was administered for all patients in both arms of the study.

3.2.2 Study population

Consecutive consenting patients with triple vessel or left main stem coronary artery disease undergoing on-pump coronary artery bypass graft surgery at the CMJAH, were recruited for this study. Ethical approval (Appendix 1) for the study was obtained from the Human Research Ethics Committee of the University of the Witwatersrand. Informed written consent (Appendix 2) was obtained from patients willing to participate in the study. The trial was registered with the Pan African Clinical Trials Registry, trial number PACTR201806003460336.

The study participants were covered by clinical trial insurance (Appendix 5). Approval for using dexmedetomidine for the trial was received from the Medicines Control Council of South Africa (Appendix 4), as it is not licensed for intraoperative use in South Africa. It is only licenced for post cardiac surgery ICU sedation. The study was conducted in accordance with the Declaration of Helsinki (98).

3.2.3 Inclusion criteria

1. Left main or triple vessel coronary artery disease.
2. Age above 18 and below 65 years.

3.2.4 Exclusion criteria

1. Age below 18 or above 65 years.
2. Pregnancy or lactation.
3. Liver dysfunction (AST or ALT > twice the upper range of normal). Normal values (National Health Laboratory Services: AST 5–40 and ALT 5–40 units/dl).
4. Sick sinus syndrome.
5. Use of concomitant medication with potential for major drug interactions such as propoxyphene, sodium oxybate and tinazide.
6. Patients requiring preoperative inotropic support.
7. Asthma.

8. Uncontrolled pulmonary congestion as evidenced radiologically and by arterial hypoxemia.
9. Evidence of ongoing infection as indicated by acute phase reaction markers.
10. Patients undergoing combined coronary and valve surgery, or other open-heart procedures.

3.3 Anaesthetic technique

1. The following interventions were performed during the preoperative visit:

- Informed consent was obtained.
- 40% supplemental oxygen by mask was given to improve oxygen supply to the myocardium.
- Midazolam 0.25–0.5 mg/kg orally with a maximum dose of 10 mg one to two hours before induction was prescribed for anxiolysis.
- Routine medication was prescribed, excluding anticoagulants and angiotensin-converting enzyme (ACE) inhibitors – to reduce the risk of perioperative bleeding and hypotension.

2. Intraoperative monitoring comprised the following:

- Electrocardiogram (ECG).
- Non-invasive blood pressure.
- Oxygen saturation.
- Continuous 40% oxygen supplementation.
- Depth of anaesthesia monitoring with bispectral index (BIS) monitor (from Covidien).

3. Intravenous lines were inserted as follows:

- Skin local anaesthesia with lignocaine followed by:

- 14- or 16-gauge intravenous catheter.
- 20-gauge radial artery catheter.
- 7.5 French internal jugular or subclavian (left or right) central venous pressure catheter.

4. Blood samples were obtained and frozen to be processed in a single batch.

5. Dexmedetomidine dosage:

- The standard recommended dose for dexmedetomidine is 0.3 – 0.7 μg/kg/hr. For each individual patient, the initial starting dose of the active drug or placebo prepared by the pharmacist as "drug" was 0.3 μg/kg/hr. The dose was titrated up according to blood pressure and heart rate response up to the dose of 0.7 μg/kg/hr, with particular care to giving a lower dose in patients above the age of 60 years.
- The drug was issued once before anaesthesia induction, commenced at induction and continued throughout the intra-operative period until the end of the volume (50 ml). There were therefore different cessation times depending on the patient's weight and the rate at which the anaesthesiologist chose to run the infusion and their intraoperative titration which was based on haemodynamic changes.
- For most patients, the infusion was continued for up to 2-4 hours in ICU until the syringe was empty. The plan was to run the infusion as naturally as possible as was the tradition of running intraoperative infusions in our unit. None of the patients had the infusion stopped prematurely in the intraoperative period. No additional dexmedetomidine was added in ICU as our hospital did not have the drug on schedule. Rescue analgesia and sedation was with morphine and midazolam.

6. For anaesthetic induction, the following were given intravenously:

- Propofol 0.5–1 mg/kg.
- Midazolam 0.1–0.5 mg/kg.
- Sufentanil 0.1–1 μg/kg or fentanyl 1–2 μg/kg.

- Rocuronium 0.3–1.2 mg/kg.

7. Anaesthetic was maintained with the following:

- Propofol 0.5–1 mg/kg/min.
- Midazolam 0.25–0.5 mg/kg/min.
- Sufentanil 0.01–0.1 μg/kg/min or fentanyl 1–2 μg/kg/hr or remifentanil 0.25–0.5 μg/kg/min.
- Rocuronium 0.3 mg/kg/hr.

8. Vasoactive drugs and volume resuscitation comprised the following:

- Phenylephrine bolus doses of 50–100 μg.
- Phenylephrine infusion of 50–250 ng/kg/min.
- Trinitroglycerine (TNT) infusion of 0.5–2 μg/kg/min.
- Intravenous fluid boluses of 250 ml titrated to haemodynamic goals.

9. Adjuncts for treatment of tachycardia, hypertension and arrhythmias included:

- β blocker (esmolol 0.25–1 mg/kg or labetolol 10–20 mg).
- Lignocaine 1 mg/kg to treat ventricular tachyarrhythmia.
- Calcium chloride for replacement when indicated.
- Serum potassium optimised to prevent arrhythmia.
- Atropine for brady-arrhythmias.
- Magnesium sulphate for arrhythmia prevention/treatment and free radical scavenging.

10. Cardiopulmonary bypass was conducted as follows:

- Crystalloid solution as prime, except in patients with a haemoglobin of less than 10 g/dL, in which case packed red blood cells were used.
- Pump flow rate as per the Du Bois chart used by the perfusionists (2.4–3.0 L/min/m^2).
- Myocardial preservation with warm antegrade and retrograde cardioplegia with blood and Medsol cardioplegic induction, and maintenance solution at a ratio of 4:1.
- Topical cooling of the heart with ice-cold water.
- Body temperature decreased to 30°C–32°C during aortic cross-clamping using a pump cooler.
- $PaCO^2$ (carbon dioxide partial pressure) adjusted according to alpha-stat regulation.

11. Inotropic/Vasoactive Support post-CPB comprised the following:

- Adrenaline 50–100 ng/kg/min infusion;
- Phenylephrine 50–250 ng/kg/min infusion;
- Nitro-glycerine 0.5–1.5 µg/kg/min;
- Phenylephrine boluses of 50–100 µg.

12. Blood and blood products replacement was conducted as follows:

- Blood and blood products administered as per guidelines for transfusion in an adult cardiac patient to achieve a required haematocrit and a normal clotting profile according to the "American Society of Anaesthesiology Guidelines for Transfusion of Packed Red Blood Cells in Adults" (216).

3.4 Blood sample storage

Blood samples drawn were immediately labelled with the patient's study number and taken to the laboratory, centrifuged within 1 hour and stored at –80°C until assayed in batches. Plasma was thawed later and prepared for processing.

3.5 Postoperative management

Patients were transferred to the ICU for at least 24 hours during which the study drug and blood samples, a twelve-lead ECG and haemodynamic parameters were recorded.

3.6 Blood sample analysis

Blood samples stored as per instructions in Appendix 3 were assayed in batches. The procedure involved thawing of samples to temperatures of 16°C–25°C. Two mL were taken for sampling and the remainder was refrozen and stored. The following assays were performed:

Hs-cTnT: "Test principle was a two-site sandwich immunoassay. When the specimen was added to the sample pad, it moved through the conjugate pad and mobilised gold anti-cTnT conjugate that was coated on the pad. The mixture moved along the membrane by capillary action and reacted with anti-cTnT antibody that was coated on the test region. If cTnT was present at detectable levels, the result was the formation of a coloured band in the test region. If there was no cTnT in the sample, the area remained colourless. The mixture continued to move to the control area and formed a pink to purple colour, indicating the test was working and the result was valid." (217)

CRP: "The test was based on an immunological reaction between CRP antisera bound to biologically inert latex particles, and CRP in the test specimen. When serum containing more than 0.8 mg/dL CRP was mixed with the latex reagent, visible agglutination occurred. The aggregates were then determined turbimetrically." (218)

NT-proBNP: “In the first step, biotin-labelled and ruthenium-labelled polyclonal sheep antibodies (binding to different regions of NT-proBNP) were combined with 20 µL of sample and incubated for 9 minutes. In the second step, streptavidin-coated magnetic microparticles were added and the mixture was incubated for a further 9 minutes. After the second 9-minute incubation, the reaction mixture was transferred into the measuring cell where the beads were captured on the surface of an electrode by a magnet. Unbound label was removed by washing the measuring cell. In the last step, voltage was applied to the electrode in the presence of a tripropylamine-containing buffer and the resulting electrochemi-luminescent signal was recorded by a photomultiplier. Pure NT-proBNP peptide in analyte-free human serum matrix was measured” (219). Samples were analysed using ROCHE test assay through the NHLS.

Interleukins: “An enzyme linked immunosorbent assay (ELISA) test based on standard sandwich enzyme-linked immune-sorbent assay technology was used. The interleukin-specific polyclonal antibodies were precoated onto plates with wells. The human-specific detection polyclonal antibodies were biotinylated. The unknowns and biotinylated detection antibodies were added to the wells and followed by washing with a prepared buffer. A peroxidase complex was added and unbound conjugates were washed away with the prepared buffer. A colour change was shown by adding an acidic stop solution. The density of the colour was proportional to the human interleukin amount captured on the plates. For this analyte, IL-6 levels below 0.01 pg/mL and IL-10 below 3.64 pg/mL were undetectable. Interleukins were analysed with Doctor R. Duarte using reagent: LXSAHM–02 – Human Magnetic Luminex Screening Assay, panel reference number 6Rl x HCGD from Whitehead Scientific (Pty) Ltd.” (220)

3.7 Outcome measures

3.7.1 Primary outcome

1. Postoperative serum hs-cTnT measured 24 hours post induction.

3.7.2 Secondary outcomes

1. Change in serum hs-cTnT 24 hours post induction and hs-cTnT at baseline.

2. Postoperative serum IL-6 and IL-10.
3. Preoperative IL-6 and IL-10 and the change in IL-6 and IL-10 over 24 hours.
4. Length of ICU stay (days).
5. Length of hospitalisation (days).
6. 30-day postoperative mortality.
7. 1-year mortality.
8. Predictive value of dexmedetomidine administration, preoperative inflammatory marker CRP and cardiac biomarkers hs-cTnT (baseline and at 24 hours) and NT-proBNP towards length of ICU stay; length of hospitalisation; and 1-month mortality.

3.8 Statistical analysis, sample size and power estimates

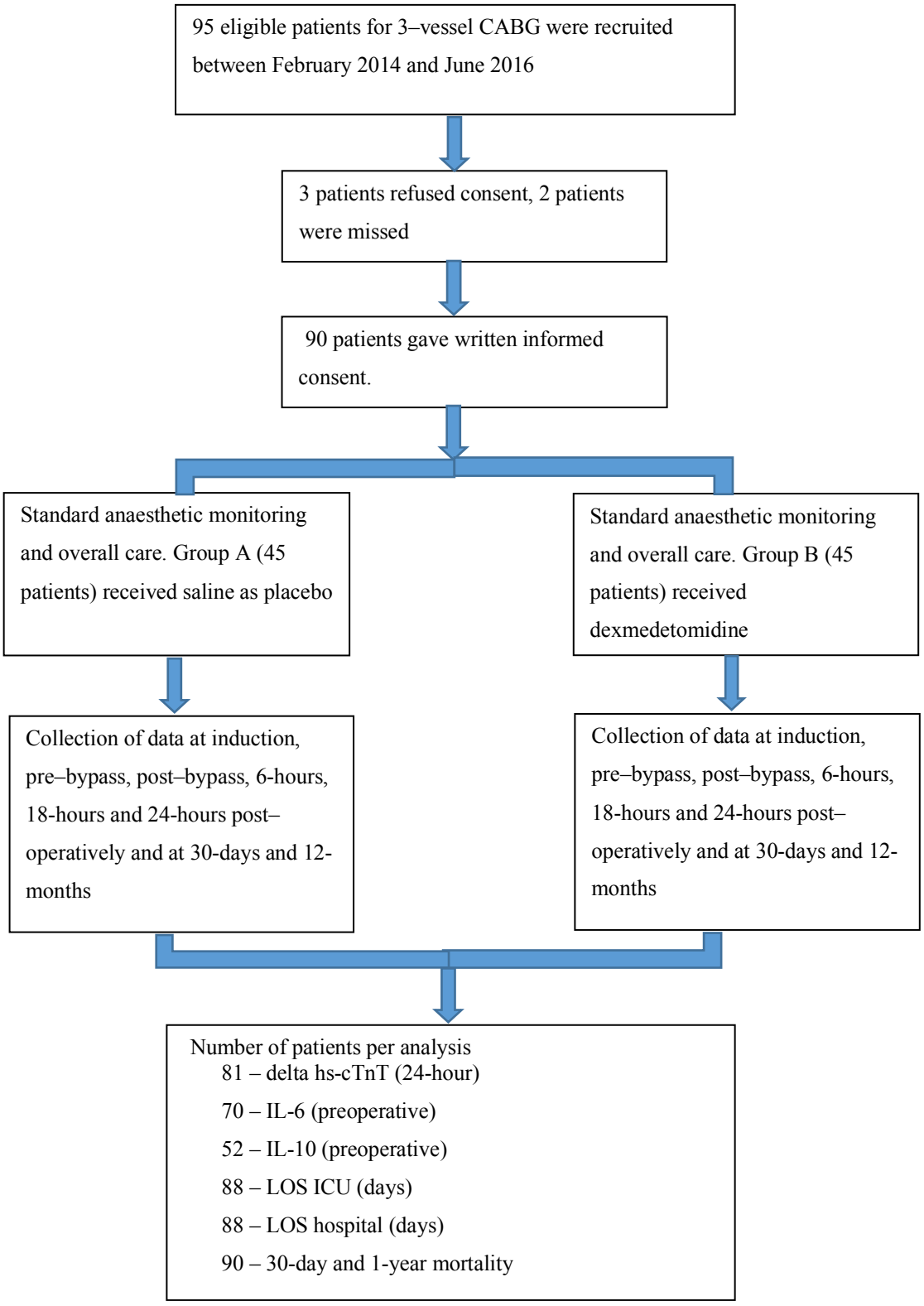
The sample size calculation was based on previous work on cTnT tests, as at time of this estimation there was no study published that had used hs-cTnT in evaluating the effects of dexmedetomidine in CABG surgery. A post-hoc sample size and power analysis are performed and reported.

From these studies, it was estimated that mean cTnT levels of 1.3 and 0.4 ng/ml with a standard deviation of 1.5 ng/ml in each arm (placebo vs. dexmedetomidine, respectively), would be significant. This study assumed that a two-tailed t-test, at $\alpha = 0.05$ for independent samples would be used to compare mean troponin levels in the 2 groups.

Assuming these estimates, a minimum sample size of 40 per arm was required in order to achieve a power of 80%. Five participants were added on to each arm of the study to allow for loss to follow-up. Data analysis was performed using Stata/SE 13.1 statistical software (Copyright 1985–2013 Stata Corp LP Statistics/Data Analysis Stata Corp 4905 Lakeway Drive Special Edition College Station, Texas 77845 USA 800–STATA–PC http://www.stata.com, stata@stata.com).

Normally distributed data was presented as mean and standard deviation whereas skewed data was presented as median and interquartile range for skewed distribution. Comparative statistics were used to analyse the two study subsets using paired and unpaired Student's t-test for parametric data or Mann-Whitney and Wilcoxon matched pairs for nonparametric data. Anova and Kruskal Wallis tests were used to compare 3 and more, normally distributed and skewed data sets, respectively. Correlations were determined by Pearson's and Spearman's test for parametric and nonparametric data respectively.

Categories were plotted on a contingency table and analysed as proportions using the Fisher's exact test. Multilinear and logistic regression analysis models were used for continuous and binary independent outcome variables respectively to look for associations between patient variables. Regression diagnostics were performed. Simultaneous quantile regression was used due to failure of the data to comply with regression diagnostics. Randomisation scheme is schematically shown in Figure 3.1.



*sample sizes for individual analysis are also indicated in respective datasets

Figure 3.1: CONSORT randomisation flow chart

CHAPTER 4 : DEXMEDETOMIDINE vs PLACEBO

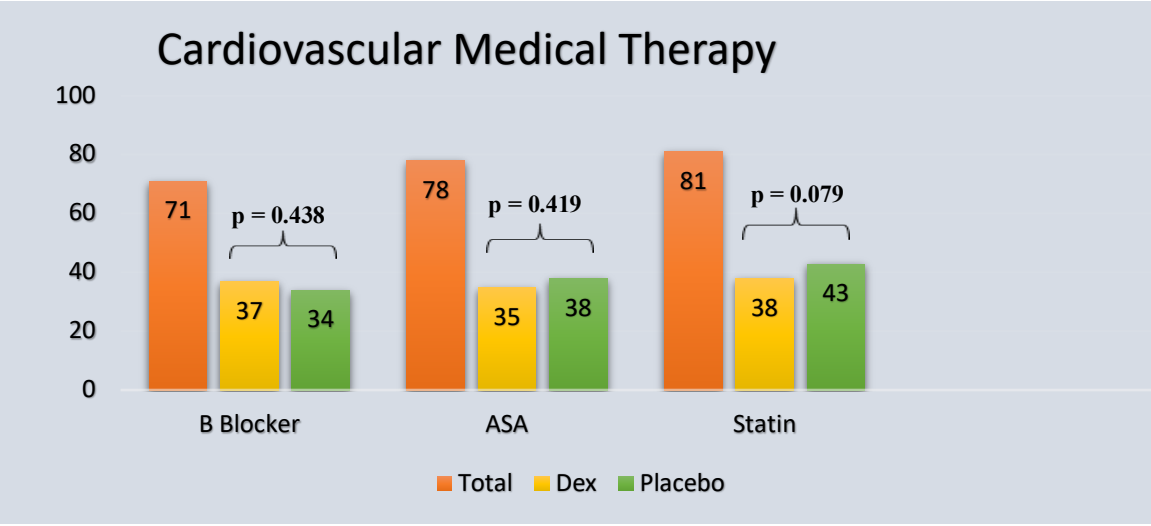
4.1 Introduction

Conventional cTn has increased sensitivity and analytical performance in detecting myocardial injury. Hs-TnT is postulated to have greater sensitivity compared with cTn in detecting myocardial injury. In light of this, we sought to describe the effect of dexmedetomidine on hs-cTnT levels post CABG surgery. This chapter reports the results of the clinical trial to this effects.

4.1.1 Baseline characteristics: dexmedetomidine vs placebo

The baseline characteristics and preoperative risk factor profile between the two groups are detailed (Figure 4.1) (Table 4.1).

Gender and ethnicity were comparable between groups. There was no difference in risk factor profile. The proportions of patients on cardiovascular medical therapy were the same in the two groups (Figure 4.1). There was no significant difference in Aocx and CPB time between the two groups (Table 4.1). The number of vessels grafted was also comparable.



β Blocker – Beta Blocker; ASA – Acetylsalicylic Acid; Dex – Dexmedetomidine; total – number of patients out of 90 on cardiovascular medication; β Blocker (p = 0.438), ASA (p = 0.419), Statin (p = 0.079)

Figure 4.1: Patients on cardiovascular medical therapy

Table 4.1: Characteristics differences between dexmedetomidine and placebo

Parameter	Dexmedetomidine (n=45)	Placebo (n=45)	p value
Age (yr) median(IQR)	57(51–60)	57(51–61)	0.8524
Africans n(%)	9(20)	10(22)	0.7973
Female n(%)	11(24)	7(16)	0.7973
NYHA mean(SD)	2.61(0.840)	2.52(0.86)	0.6443
*EF (%) median(IQR)	55(45–60)	50(45–57.5)	0.0533
Weight (kg) median(IQR)	81(67–90)	79(71–93)	0.7043
BMI (kg/m^2) median(IQR)	27(24–30)	28(24–32)	0.2661
Smoking n(%)	24(53)	18(40)	0.2050
Dyslipidaemia n(%)	25(56)	25(56)	1.0000
Hypertension n(%)	35(78)	34(76)	0.8030
Diabetes Mellitus n(%)	21(47)	18(38)	0.3930
Aocx time (min) mean(SD)	109.28(27.20)	105.82(28.03)	0.5532
CPB (min) mean(SD)	155.93(32.17)	152.77(43.66)	0.4290
Number of vessels mean(SD)	2.93(0.65)	2.91(0.76)	0.8824

*Ejection fraction was analysed in only 82 patients as we did not have data on the remaining 8 patients.
BMI – body mass index; EF – ejection fraction; NYHA – New York Heart Association functional class; Aocx – aortic cross-clamp time in minutes; CPB cardiopulmonary bypass time in minutes; Vessels – number of vessels grafted; and yr – year

4.1.2 Effects of dexmedetomidine on hs-cTnT

Eighty-one patients were analysed for hs-cTnT biochemical tests. Forty in the dexmedetomidine group and 41 in the placebo group. Two patients died on the operating table.

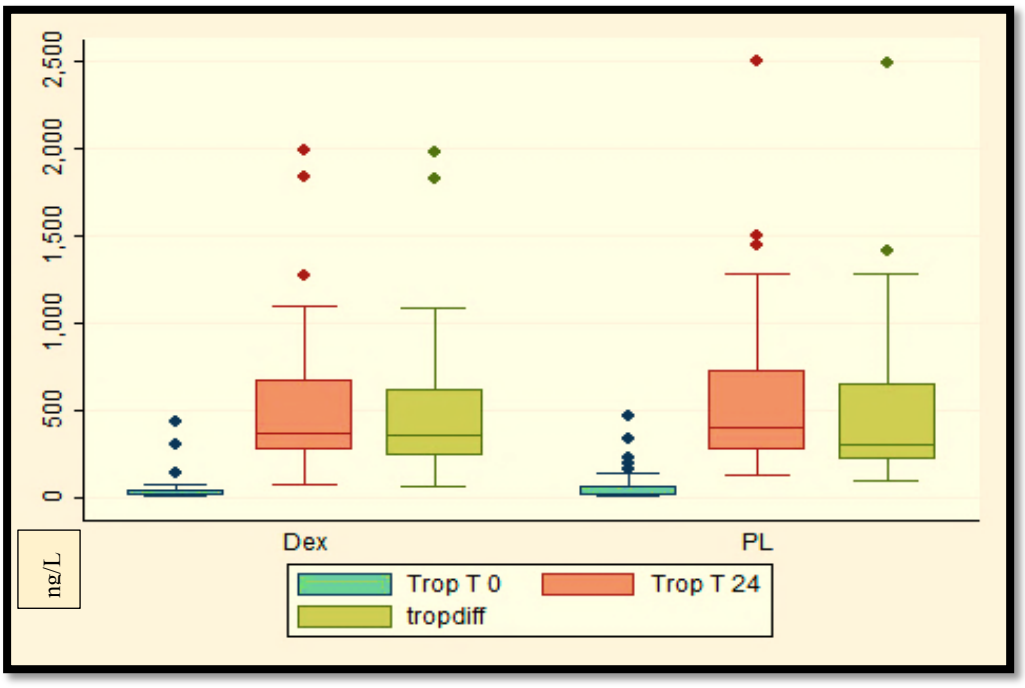
There was a statistically significant increase in hs-cTnT from baseline to 24 hours post induction, 13(8–38) ng/L vs. 367(266–691) ng/L respectively ($p < 0.001$) (Table 4.2). The

change in hs-cTnT from baseline to 24 hours (delta hs-cTnT) was not statistically different between groups: 353.5(231.5–621.5) ng/L vs. 301(217–648) ng/L, p = 0.59, placebo and dexmedetomidine respectively (Figure 4.2).

Table 4.2: Troponin at baseline and 24 hours

Hs-cTnT (ng/L) median(IQR)	Baseline	24-hour	p value
Total (Dex + placebo) (n=81)	13(8– 38)	367(266– 691)	<0.001
Dexmedetomidine (n=40)	12(8.5– 34)	365(272.5– 669)	<0.001
Placebo (n=41)	12(7– 62)	393(266– 721)	<0.001

Hs-cTnT – high-sensitivity cardiac troponin T, between baseline and 24-hour troponin



Dexmedetomidine (Dex) and placebo (Pl): hs-cTnT at Baseline – Blue (T0); hs-cTnT at 24-hour (T24) – Red; and delta hs-cTnT (tropdiff) – Green (difference between induction and 24-hour levels)

Figure 4.2: Comparison between dexmedetomidine and placebo

The comparison of Troponin levels 24 hours post induction between the two groups was not statistically significant 365(272.5–669) ng/L vs. 393(266–721) ng/L, p = 0.94, dexmedetomidine and placebo respectively (Figure 4.2).

4.1.3 Effects of dexmedetomidine on interleukins

Analysis of IL-6 was undertaken in 70 patients, whereas that of IL-10 was undertaken in 52 patients. The remaining patients could not be assayed for these cytokines because either their samples clotted during processing or results were undetectably low and out of range for the reagent. The results of the interleukin levels at induction were abandoned because, although they were processed, the majority reported out of range levels (too low) for this reagent as well.

There was no significant difference at 24 hours in IL-6 between the dexmedetomidine and placebo groups 0.1(0.06–0.15) pg/ml vs. 0.09(0.06–0.17) pg/ml, p = 0.42, respectively. Furthermore, dexmedetomidine did not influence levels of IL-10 when compared with placebo 4.45(3.2–7.48) pg/ml vs. 4.39(1.69–8.39) pg/ml, p = 0.41 (Table 4.3).

Table 4.3: Comparison between IL-6 and IL-10 at 24-hour postinduction between dexmedetomidine and placebo

Interleukin (pg/mL)	Total	Dexmedetomidine	Placebo	p value
	(n = 70)	(n = 34)	(n = 36)	
IL-6 median(IQR)	0.10(0.06–0.17)	0.09(0.6–0.17)	0.1(0.06–0.15)	0.9812
	(n = 52)	(n= 25)	(n = 27)	
IL-10 median(IQR)	4.42(2.18–7.65)	4.45(3.2–7.48)	4.39(1.69–8.39)	0.3791

IL-6 – interleukin 6; IL-10 – interleukin 10; total – results for the whole sample

4.1.4 Effects of dexmedetomidine on length of stay in ICU

There was no significant difference in LOS in ICU between the two groups 3(2–4) vs. 3(2–4) days, p = 0.33 (Table 4.4). Fewer patients (48%) in the dexmedetomidine group stayed in ICU for 3 days of fewer, compared with the placebo group (56%). The maximum number of days in ICU was 28 and 15 in the dexmedetomidine and placebo groups, respectively.

4.1.5 Effects of dexmedetomidine on hospital stay

Patients who received dexmedetomidine stayed in hospital for longer. The difference in hospital stay was statistically significant: 8(7–11) vs. 8(6–10), p = 0.044, dexmedetomidine and placebo respectively (Table 4.4). One patient in the placebo group stayed in hospital for 99 days. This long hospital stay was attributed to complications of sepsis. Exclusion of this patient from the analysis yielded an even stronger evidence of longer hospitalisation in those who received dexmedetomidine (p = 0.025).

Table 4.4: Length of stay in ICU and hospital

Group	median (IQR)	min – max	p value
	*ICU stay (days)		
Dexmedetomidine (n=44)	3(2–4)	0–28	
Placebo (n=44)	3(2–4)	0–15	0.3319
	Hospital stay (days)		
Dexmedetomidine (n=44)	8(7–11)	0–45	
Placebo (n=44)	8(6–10)	0–99	0.0439

*Two patients died on the table, one each from the dexmedetomidine and placebo groups prior to ICU admission.

With consultation with the cardiothoracic team in the institution, a decision was made that normal hospital stay is approximately 6 days post CABG surgery. Categorising hospital stay into “normal stay = 6 days" and “long stay > 6 days”, showed that more patients in the placebo group (31%) had a ‘normal stay” compared with 9% of patients in the dexmedetomidine group. Importantly, we included LOS ICU in the calculation of overall

length of hospital stay. It is therefore possible that in some cases this time (hospital LOS ≤ 6 days) could have been spent in ICU. Eight patients in the whole study group stayed in hospital for more than 15 days.

To exclude the effects of renal dysfunction as a cause for prolonged hospital stay in patients receiving dexmedetomidine, a subanalysis was performed. Those patients in the dexmedetomidine group that developed acute kidney injury (AKI) as per the kidney disease improving global outcomes (KDIGO) criteria, stayed in hospital for 8.5(7.5–15) days compared with those who didn't, 8.5(7–11) days, p = 0.2119.

4.1.6 Effects of dexmedetomidine on 30-day and 1-year mortality

Four patients died within 30-days, in addition to those who died on the operating table. Three patients 3(7%) were in the dexmedetomidine group and 1(2%) patient was in the placebo group. The difference was not statistically significant (p = 0.31).

Eighty-six patients were followed up for an analysis of 1-year mortality. A total of 9 patients died (mortality rate of 10%). Of the 9 patients, 5(11%) were in the intervention group and the other 4(9%) were in the placebo group. The probability of mortality at 30 days and in 1 year was not different (RRR 3; 95% CI 0.3, 27.76; p = 0.1263) and (RRR 1.25; 95% CI 0.36, 4.35; p = 0.38) respectively. The current study was powered for cTn outcome and therefore the mortality analysis is underpowered.

4.1.7 Effects of dexmedetomidine on adverse events

This analysis excludes the four patients that died. In total, 13% of patients had adverse events (any untoward events in the patients during the drug trial leading to prolonged length of stay or mortality which may not necessarily have had a causal relationship with this intervention) (Table 4.5). Six patients (7%) patients were placed on extracorporeal/mechanical haemodynamic support (intra-aortic balloon pump or extracorporeal membrane oxygenator) in the perioperative period and the majority (4 out of 6 patients) were in the dexmedetomidine group. The difference was not statistically significant (p = 0.398).

AKI, defined as an increase in serum creatinine by 0.3 mg/dl or more within 48 hours, as per the KDIGO clinical practice guidelines/criteria, occurred in 16(22.9%) patients. The rate of AKI between those who received dexmedetomidine and placebo was not significantly different (23.5% vs. 22.2%, p = 0.918 respectively). Eleven patients were found to be in stage 1, four in stage 2, and one in stage 3 of the KDIGO AKI severity classification.

Hepatic function tests were not routinely investigated. There were no reports of respiratory infections in the perioperative period. Sepsis-related complications were related to sternal wound and leg infections (Table 4.5). The other adverse events observed were bleeding, wound sepsis, and overt neurological fallout.

Table 4.5: Adverse events by drug

Intervention	Dexmedetomidine (n=42)	Placebo (n=44)	p value
Bleeding n(%)	2(4.6)	1 (2.4)	0.584
Sepsis n(%)	4(9.5)	3(6.8)	0.646
Neurological n(%)	1(2.4)	0(0)	0.303
*AKI n(%)	8(23.5)	8(22.2)	0.918
Mechanical support n(%)	4(8.9)	2(4.4)	0.398
Total events n(%)	19(45)	14(31)	0.09

AKI – acute kidney injury, (*Dexmedetomidine n=34 and placebo n=36)

4.2 Reliability of data

The post-hoc estimated power for a mean difference of 52.5 ng/L change in hs-cTnT for a sample size of 81 and a two-sided α of 0.05 was 62%. Based on this difference an estimated optimal sample size of over 122 with at least 62 patients in each group would show a power of 80% and a two-sided α of 0.05 for hs-cTnT. Similarly, the outcome on hospital stay was underpowered and would have needed an estimated sample size of 183 patients with 92 per group for a power of 80% and a two-sided α of 0.05.

The optimal sample size based on the event rate for 30-day mortality of 2% in the placebo group and 7% in the dexmedetomidine group (difference of 5%), would have needed 269 patients in each group to obtain a power of 80% and a two-sided α of 0.05. For a reduction in event rate of 1-year mortality with a power of 80% and a two-sided α of 0.05 given a difference of 2% (9% placebo and 11% dexmedetomidine) in this study, an estimated total sample size of 7053 patients with an estimated 3527 patients per group would have been needed.

4.3 Discussion

4.3.1 Dexmedetomidine and ischaemic marker hs-cTnT

The present study, unlike previous studies, made use of hs-cTnT to assess the extent of myocardial injury in patients undergoing CABG surgery. This biomarker has been shown to be more sensitive in the diagnosis of ischaemia than conventional cTn assays used in other studies (221). There was a statistically significant increase in hs-cTnT at 24 hours postsurgery compared with the level at baseline in the whole group of this current study. However, there were no significant differences between the dexmedetomidine and placebo groups (difference in means of 52.5 ng/L). Despite the sensitivity of the biomarker used, the difference was not statistically significant. Similar findings were seen in previous studies that used conventional cTn (14, 106, 178).

The possibility of the result being influenced by the small sample size should be born in mind as this study was shown to be underpowered at 62% in a post-hoc power estimation. As there are no reports on the effects of dexmedetomidine on hs-cTnT in CABG surgery, this study serves as a benchmark from which future studies can be built. A larger sample size estimated to be over 122 with at least 62 patients in each group for a power of 80% and a two-sided α of 0.05 would yield more reliable results. Previous studies using conventional cTn were also small. This warrants a meta-analysis.

Bulow *et al.* (106), using mini-CPB with no confounding anaesthetic agents, did not find significant differences in ischaemic markers between their dexmedetomidine and placebo groups using cTnI. Apart from the use of mini-CPB, their study method was similar to our study. Similarly, Ren *et al.* (166) found no difference in the increase in cTnI levels in OPCAB patients between groups at 24 hours. Of the types of coronary artery bypass graft surgery, full CPB is expected to lead to raised cTn levels compared with mini-CPB and OPCAB.

Similarly, two studies by Kundra *et al.* (222, 223); one on patients with normal coronary vessels and the other on patients with CAD, using cTnT, found no difference in outcomes. During cardiac catheterisation, they measured levels of cTnT at 6, 12 and 24 hours post procedure. They showed no difference in cTnT at all measurement points between the dexmedetomidine and placebo groups, in both normal and CAD patients. They, however, confirmed evidence of epicardial coronary arterial vasoconstriction as previously reported in a preclinical study by Roekaerts *et al.* (161).

Of note is that, in the study by Kundra *et al.* (223), dexmedetomidine was used without the addition of any anaesthetic agent that has the potential of cardioprotection – similar to this current study, as these drugs tend to confound the results when used together with dexmedetomidine (31, 177, 180, 224). Furthermore, Kim *et al.* (178) did not find attenuation of ischaemic markers when dexmedetomidine was compared with lignocaine in cardiac surgery. They had tested the effects of dexmedetomidine compared with lignocaine and lignocaine-dexmedetomidine. They found significant attenuation of ischaemic markers with lignocaine and lignocaine-dexmedetomidine but not with dexmedetomidine on its own.

The addition of a cardioprotective and/or anti-inflammatory agent in the treatment regimen may have an influence on the effects of dexmedetomidine on ischaemic markers. Riha *et al.* (181) added ketamine to dexmedetomidine in their study and compared these two drugs with sufentanil-sevoflurane. They found significant decreases in the levels of cTnI and CKMB in the ketamine-dexmedetomidine combination.

In another study by Chi *et* al (177), morphine was added as premedication in the dexmedetomidine and placebo groups with no resultant difference in ischaemic markers between groups. Morphine is also known for its cardioprotective effects (3).

Sevoflurane was added on both arms of trials by Chen *et al.* (15) and Tosun *et al.* (11, 180) when comparing dexmedetomidine with placebo, with inconclusive results. Sevoflurane is known for its effects in enhancing myocardial preconditioning (75, 145, 146). The conduct of anaesthesia in the above-mentioned two studies was similar apart from the addition of dexamethasone as an adjunct to Tosun *et al.*'s (180) anaesthetic regimen.

Tosun et *al.* (180) found no difference in ischaemic markers in contrast to Chen *et al.* (15), who found a reduction in ischaemic markers in the dexmedetomidine group with the addition of sevoflurane only and no additional anti-inflammatory agent. The question, therefore, is whether addition of dexamethasone, a stress hormone with anti-inflammatory and immunosuppressive effects, may have had enough influence to result in a different outcome compared to the findings of the study by Chen et *al.* (15). This addition of dexamethasone on both arms of the trial by Tosun *et al.* (180) may have confounded the effects of dexmedetomidine, which is postulated to also have anti-inflammatory effects.

The ischaemic marker measurement time-points used differ from study to study, making comparison difficult. Several RCTs investigated the effects of dexmedetomidine in CABG surgery by employing kinetic measurement of ischaemic markers (106, 177, 180). The kinetic measurements from these RCTs present non-uniform data with inconclusive interpretation. In agreement with our study, these studies using kinetic analysis, found no difference in ischaemic markers at the 24-hour measurement point (106, 177, 180).

Fellahi *et al.* (114, 117) showed that prediction of outcome with a single 24-hour troponin measurement provided an accurate enough analysis without the complexity of performing and interpreting kinetic or integrated area under the curve analysis. Testing at earlier time periods post-CPB could also be subject to interference by haemodynamic, metabolic and elimination

disturbances (45). It is for this reason that in this current study we chose to measure troponin levels 24 hours post CPB.

In analysing studies that investigated the effects of dexmedetomidine on ischaemic markers, one has to interrogate the different dosing regimen used. While some used clinically recommended dose titration methods, others used fixed doses. Some studies looked a high dose whilst others looked at low doses (177). Their outcomes seem different depending on the dose regimen used. This is reflected clearly in preclinical and clinical studies (159, 177) that specifically looked at this matter.

A statistically significant difference in troponin levels at 48 hours was found by Chi *et al.* (177) with the "high" dexmedetomidine regimen. Okada *et al.* (159) also showed that a dose equivalent to 2.3 ng/ml achieved significantly better outcomes than a lower dose of 0.23 ng/ml. These two studies used the fixed-dose infusion method. Our study used recommended clinical doses of 0.3–0.7 μg/kg/hr titrated to effect and did not find favourable results. Therefore, it is unclear whether some benefit could have been derived from using a higher fixed regimen.

Several other studies showed that a dosing method similar to the current study did not yield significant differences in ischaemic markers (106, 178, 180). This dosing method is one used in normal clinical practice. A study by Jones *et al.* (225), in an ICU setting, showed that the effects of dexmedetomidine at doses above 0.7 μg/kg/hr did not increase benefit. The limiting factor is also the effects of dexmedetomidine on heart rate and blood pressure (99).

Of importance, also, is the timing of drug commencement and discontinuation in relation to ischaemia-reperfusion. To explore this issue, a preclinical study by Mimuro *et al.* (160) highlighted this effect on area of infarct. When testing for the effects of dexmedetomidine on global ischaemia, they looked at the impact of administering dexmedetomidine post the ischaemia-reperfusion period. This phenomenon is similar to that experienced by patients during CPB. In their study, dexmedetomidine worsened infarct size when compared with

control. In the current study, dexmedetomidine was administered continuously from induction until arrival in ICU. We did not explore how this may have affected outcome.

It has been shown that dexmedetomidine vasoconstricts epicardial vessels (190, 223). Preclinical studies used 30-minute intervals of ischaemia to confer preconditioning. In clinical trials, including the current study, the initiation and discontinuation points differed (99, 106, 170, 177, 180, 181). It has not been shown if differences in initiation and discontinuation points influenced outcomes.

Talke *et al.* (164) with vascular patients at high risk of CAD, administered dexmedetomidine for 48-hours postsurgery. Apart from better haemodynamic parameters within the dexmedetomidine groups, they found no difference in ischaemic markers when compared with placebo. Their postoperative patient management was in stark contrast to the standard postoperative treatment of cardiac and vascular patients in clinical practice. With the advent of fast-track cardiac surgery, it would be difficult to incorporate this in clinical practice (226). They found no differences between the groups in postoperative major adverse cardiac events, despite this practice.

Patients who undergo CPB-supported CABG surgery experience ischaemia-reperfusion, and a heightened level of inflammatory response. OPCAB patients are different in this regard when compared with CPB patients. This is also true for patients undergoing noncardiac surgery. A meta-analysis by Biccard *et al.*(10) found no significant reduction in myocardial ischaemia with dexmedetomidine in noncardiac surgery, however it was underpowered.

OPCAB studies show very conflicting results. Ren *et al.* (166) found a statistically significant decrease in markers at 12 hours postsurgery, but found no difference at 24, 48 and 72 hours postsurgery in their OPCAB cohort. The attenuation of troponin and CKMB at 12 hours did not translate into better clinical outcomes. On the contrary, Chi *et al.* (177) found a significant difference in 48-hour ischaemic-marker level postsurgery in their OPCAB cases. They also found an unexplained statistically significantly prolonged intubation and LOS in ICU in the

dexmedetomidine group. OPCAB surgery involves intense haemodynamic changes due to positioning of the heart, affecting multiorgan perfusion. These events could have an impact on the pharmacodynamics and kinetics of dexmedetomidine.

CPB studies do not seem to provide conclusive evidence on the effects of dexmedetomidine towards ischaemic markers. This is shown in the different results obtained by Tosun *et al.* (170, 180) and Chen *et al.* (90). Tosun's group (89), found no differences in CKMB, cTnI and NT-proBNP levels for all measurement intervals whereas Chen and colleagues (90) found a 2-fold decrease in enzymes at 2 hours, and a 1.6-fold decrease in enzymes at 24 hours post cross-clamping. The differences in these two studies are difficult to explain from an anaesthetic point of view.

Addition of lignocaine, ketamine and dexamethasone was shown to affect outcome (178). This current study may therefore be a confirmation of the study by Bulow *et al.* (106, 227, 228) in that dexmedetomidine, in the absence of cardioprotective anaesthetic agents and in patients on CPB, does not attenuate the increase in ischaemic markers.

4.3.2 Dexmedetomidine and inflammatory markers

The present study found no difference in IL-6 and IL-10 at 24 hours post induction in CABG surgery patients in either the dexmedetomidine or the placebo group. The preoperative IL-6 and IL-10 results could not be analysed as for most patients they were below the range for the reagent used.

The results of this current study are similar to those found by Farsad *et al.* (172). In 61 patients randomised to dexmedetomidine and placebo, they found no difference in the levels of IL-6 or IL-10. Of concern is that they found an increase in TNF-α in the dexmedetomidine group.

Ueki *et al.* (171), on the other hand, found no difference in TNF-α and CRP levels at 24 hours post CPB. Riha *et al.* (181), while comparing ketamine-dexmedetomidine with sufentanil-sevoflurane, found a reduction in IL-6 levels postoperatively in the ketamine-dexmedetomidine group. One cannot conclude that the effects were solely due to dexmedetomidine use in this case. Ketamine has been shown to have significant anti-inflammatory effects on its own (183).

The interleukin results in the current study are presented as levels at a single time point (24 hours post operation). Numerous studies presented their results as a rate of increase in interleukins level, and mean differences between two time periods (106, 171). Studies using this method found a significant difference in the rate of increase of pro-inflammatory marker IL-6 at 24 hours postoperatively (106, 171). They also reported a significant reduction in TNF-α and an increase in IL-10.

Although Ji *et al.* (14), in their retrospective study, found favourable results for dexmedetomidine, the groups they compared had statistically significant heterogeneity. The preoperative clinical and perioperative factors that were significantly different in their groups had the potential to influence the results on their own. These factors were congestive cardiac failure (CCF), perioperative MI, CPB time, diabetes and EF (185, 187, 229). They used propensity score matching (PSM) to balance the two groups.

King and Nielsen (230), however, made a strong case against PSM. In their own words: *"PSM, as it is most commonly used in practice (or with many of the refinements that have been proposed), increases imbalance, inefficiency, model dependence, research discretion, and statistical bias at some point in both real data and in data generated to meet the requirements of PSM theory. In fact, the more balanced the data, or the more balanced it becomes by pruning some observations through matching, the more likely PSM will degrade inferences — a problem we refer to as the PSM paradox. If one's data are so imbalanced that making valid causal inferences from it without heavy modelling assumptions is impossible, then the paradox we identify is avoidable and PSM will reduce imbalance but then the data are then not very useful for causal inference by any method."*

A meta-analysis of the effects of dexmedetomidine on inflammatory markers clarified the controversy of differences in methodology by subgroups analysis according to type of surgery; length of surgery; dose of dexmedetomidine; length of anaesthesia; and timing of dexmedetomidine administration (169). The subgroup analysis found no difference in mean difference in changes in interleukin levels from baseline. In particular, a subanalysis of 4 studies included in the cardiac surgery group showed no difference in inflammatory marker mean difference. There was, however, significant heterogeneity in the studies included.

These results confirm the findings of this current study: dexmedetomidine does not appear to modulate the inflammatory response during cardiac surgery.

4.3.3 Dexmedetomidine and ICU stay

In the current study we found no difference in length of ICU stay between the dexmedetomidine and placebo groups. The effects of dexmedetomidine on LOS in ICU were reported in days and not in hours. This might be a shortcoming of this current study as it is difficult to compare ICU stay in this way with most other studies in the literature.

In the setting of the current study, the LOS (measured in number of hours) in ICU was difficult to work out as there were numerous factors affecting the transit time of patients from ICU to the ward. Often, it could be hours before a patient is physically transferred to the ward due to difficulties with physical bed availability in the receiving ward. The patient would still be transferred on the same day but not immediately after a discharge was ordered. Most of the studies that report on ICU stay have looked at hours instead of days. The difference between this current study and previous studies may have been influenced by our measurement of LOS in ICU in days rather than hours and this should be taken into consideration when comparisons are made.

However, our results are consistent with a study by Bulow *et al.* (106), where no significant difference in ICU stay in days was found between their TIVA and TIVA-dexmedetomidine groups. Bulow *et al.* (106) also conducted their study in tandem with this current study by not

adding cardioprotective and anti-inflammatory anaesthetic agents in their anaesthetic methods. Similarly, a study by Kim *et al.* (178) comparing dexmedetomidine and lignocaine, also found no difference in ICU stay in days between groups.

Neither did three studies that recorded ICU stay in hours find a significant difference in ICU stay post cardiac surgery (181, 231, 232). Contrary to these studies, Chi *et al.* (177) found a significant increase in ICU stay in hours in their "high" dose dexmedetomidine group. This "high" dose is in fact within the recommended anaesthetic dose. Cheng *et al.* (188), in a single-centre retrospective review of 505 cardiac patients on CPB, found that dexmedetomidine statistically significantly increased ICU stay when compared with those that did not receive dexmedetomidine perioperatively.

Studies by Ji *et al.* (14, 233) and Pasin *et al.* (231) found an association between dexmedetomidine use and a significant reduction in ICU stay. There was, however significant heterogeneity in the analysis reported in the study by Pasin *et al.* (233) and the issues with Ji *et al.*'s study have been alluded to above.

ICU studies investigating sedative effects of dexmedetomidine on outcomes are difficult to interpret. Although many reported a comparison between dexmedetomidine and placebo, there were other sedative and analgesic agents used that were not accounted for. These agents influence outcomes on length of intubation and ICU stay, and therefore should be considered to have an impact on outcome. Postsurgical, intubated and ventilated patients need both sedation and analgesia in ICU. Often the regimens used include morphine or morphine equivalents as analgesics.

A case in point is a study by Khalil *et al.* (234) which showed a significant reduction in the length of ICU stay (in hours) in the dexmedetomidine group. This study, however, reported a significant increase in the total dose of fentanyl and propofol in the non-dexmedetomidine group. Fentanyl has a prolonged context-sensitive half-time, making its effects long acting

when given as an infusion (235). This could therefore explain the increase in ICU LOS in patients that were classified as having placebo.

Maldonado *et al.* (231), investigating delirium as a primary outcome between dexmedetomidine, midazolam and propofol as comparators, found an increase in the dose of morphine equivalents in the non-dexmedetomidine groups. Herr *et al.* (236) also found a 4-fold increase in the mean dose of morphine in their propofol group when compared with dexmedetomidine. Morphine is known for its long-acting effects, and the effects of its active metabolites (3). With the exclusion of alfentanil and remifentanil, opioid agents are known to have prolonged respiratory depressant effects resulting in prolonged ventilation and subsequent prolonged LOS in ICU (235).

The sedation and analgesia protocols used by different intensive care units have an impact on measured outcomes. A defining study about this was done by Chorney *et al.* (226). In their unit, they used fast-tracking as their extubation protocol. Fast-tracking means that they used multimodal analgesia to reduce opioid use and its resultant respiratory depressant effects to facilitate shorter intubation times.

They found no significant difference in LOS in ICU in their comparison of the group that received dexmedetomidine and the one subjected to fast-tracking. Additionally, they found a significant increase in the amounts of morphine used in the dexmedetomidine group on the 1st postoperative day. A higher proportion of patients in the non-dexmedetomidine group ambulated in the first 24 hours compared with the dexmedetomidine group. They also found significant use of acetaminophen use in the dexmedetomidine group on the 2nd postoperative day.

These findings by Chorney *et al.* (226) are supported by a study by Park *et al.* (237) who used remifentanil as a dexmedetomidine sedative comparator, and found no difference in length of ICU stay, hospital stay and complication rate. This report is of importance as the drugs have

competitive pharmacokinetic profiles. Remifentanil has a short context-sensitive half-time making it an ideal comparator for dexmedetomidine (235).

Several other studies comparing the effects of dexmedetomidine with placebo or other non-analgesic agents in ICU reported the beneficial effects of dexmedetomidine in as far as time to extubation, ICU and hospital LOS are concerned (233, 234, 236, 238, 239). These studies failed to take into consideration the effects of opioid analgesics. They compared a drug that is known to have analgesic and sedative effects, reduced respiratory depressive effects and leading to reduction in morphine use, with nonanalgesic drugs. Significantly larger doses of morphine equivalents were used (233, 234, 236, 238, 239).

Khalil *et al.* (234) showed significantly lower total morphine and fentanyl use and better outcomes in patients receiving dexmedetomidine sedation in ICU. Herr *et al.* (236) showed a 4-fold increase in morphine use in their propofol comparator group compared with dexmedetomidine.

In three meta-analyses by Pasin *et al.* (233), Geng *et al.* (239), and Tan *et al.* (238), a similar pattern was followed whereby dexmedetomidine was seen to significantly reduce ICU LOS while the comparators were morphine, propofol, midazolam, haloperidol and placebo. Studies using a comparative analgesic sedative such as remifentanil were not included in these meta-analyses. All three of these meta-analyses reported significant heterogeneity of the pooled data sets in their analysis. Geng *et al.* (239) reported $I^2 = 93\%$, Pasin *et al.* (233) $I^2 = 93\%$ and Tan *et al.* (238) $I^2 = 75\%$. Studies in Pasin *et al.* (233) and Tan *et al.* (238) were not cardiac surgery studies.

In Pasin *et al.* (233), a significant number of patients in the non-dexmedetomidine groups required rescue analgesic treatment with no difference in requirements for rescue sedative agents. Although Park *et al.* (237) found no difference in extubation time, ICU stay and hospital stay when dexmedetomidine was compared with a short-acting sedative-analgesic opioid remifentanil, they found the incidence of delirium to be lower with dexmedetomidine.

Delirium was, however, shown in Maldonado *et al.*'s study (231) as the cause for longer ICU and hospital stay when dexmedetomidine was compared with midazolam and propofol. Midazolam and propofol have no analgesic effects, and morphine was therefore used as an analgesic supplement in that study.

Administration of dexmedetomidine in this current study did continue into the ICU period for some patients. The effects therefore are those of dexmedetomidine as an adjunct to anaesthesia and contributor to sedation, particularly considering its prolonged context-sensitive half-life. This study therefore concurs with similar studies that found no difference in outcome (181, 232).

4.3.4 Dexmedetomidine and hospital stay

In this study, patients who received dexmedetomidine had a longer hospital LOS. The difference was statistically significant. The number of days in hospital included the number of days in the ICU and in the ward. Duration of stay in both ICU and hospital were found to be clinically associated (240). The causes of prolonged ICU stay were found to contribute to length of hospital stay (240). The theory is supported by a multicentre study by Kramer *et al.* (241), where they showed correlation between the two parameters and also showed common causal factors in both groups.

In this current study, one data entry in the placebo group was classified as an outlier, as this hospital stay was an unexpected 99 days. An even more significant increase in LOS in hospital was seen in the dexmedetomidine group when this data entry was excluded from the analysis. This outcome cannot be explained by comparison of patient baseline and intraoperative characteristics, however, as the said patient had adverse events due to sepsis.

This result is not unprecedented, as there have been sporadic reports of an association between dexmedetomidine and prolonged LOS. Chi *et al.* (177) found a significant increase in hours on the ventilator and in ICU LOS in their dexmedetomidine group. Cheng *et al.* (188) showed a prolonged ICU LOS in the dexmedetomidine group. Using the argument by

Williams *et al.* (240) that hospital and ICU stay have common causal factors, one could say the LOS in ICU would affect LOS in hospital. On the contrary, pooled data from 4 studies in a meta-analysis by Geng *et al.* (239), showed no statistical difference in hospital stay with the use of dexmedetomidine.

The method of dexmedetomidine administration in this current study was as an adjunct to anaesthesia. The anaesthetic protocol for the two arms was standardised and similar. No dexmedetomidine was prescribed in ICU. This was adhered to as the hospital did not have dexmedetomidine available in their pharmacy and on ICU premises. The patients therefore received the same drugs in ICU.

In the ICU setting of this current study, fast-track extubation was not practiced. Fast-tracking necessitates the unit to have an armamentarium of agents with sedative and analgesic effects that allow for early extubation (226). Sedation and pain management often go hand in hand as most of the analgesic agents have both effects (235). Morphine is one such drug (235). Morphine, midazolam and perfalgan (intravenous paracetamol) were used in the ICU setting of this current study. The analgesic-sedative regimen included a very short-acting opioid remifentanil. Remifentanil is known to cause rebound pain (242). In such cases morphine, as part of the regimen, would be introduced gradually towards the intended time of tracheal extubation (242). Morphine is long-acting and has active long-acting metabolites (242).

Contrary to this current study, Brandao *et al.* (243) found a significant reduction in hospital stay in their dexmedetomidine group, while their placebo group had significantly higher Euro-scores, age and CPB time. Ji *et* al (14) also found similar results, similarly in non-homogenous groups. The increased LOS in hospital in this current study cannot be explained by the rate of adverse events. There was no significant difference in this rate when the two groups were compared. The baseline characteristics of the patients were also similar. The patients in this current study received a combination of morphine, perfalgan, remifentanil, midazolam and propofol in ICU as part of their sedation-analgesia regimen.

A subsequent simultaneous quantile regression analysis, which is reported on later in this current study to further explore this effect, showed a significant association between dexmedetomidine use and LOS in hospital in the first 7 days. Since the LOS in hospital was inclusive of ICU LOS, and the mean ICU LOS was 3.8(3.3) days, it is possible that this statistic is somewhat reflective of the time spent in ICU.

In this current study, ICU sedation and analgesia practices were not protocol-driven. These drugs have different half-lives. Dexmedetomidine has a relatively long context half-life (250 min after an 8-hour infusion) when compared with propofol and remifentanil (244). This current study is therefore reporting findings similar to those by Cheng *et al.* (188) and Chi *et al.* (177) and are in agreement with their finding of an inexplicable significant increase in ICU LOS in the dexmedetomidine group.

4.3.5 Dexmedetomidine and mortality

Four patients died in a 30-day period, postoperatively. Three patients (7%) were in the dexmedetomidine group and one (2%) patient in the placebo group. The difference was not statistically significant. Of the 90 patients, 9 (10%) patients had died at 1-year postsurgery. Five patients (11%) were in the dexmedetomidine group while four patients (9%) were in the placebo group. The relative risk ratio for both 30-day and 1-year mortality was not statistically significantly different.

In two separate randomised, controlled trials, Kim *et al.* (178) and Riha *et al.* (181) found no difference in 30-day mortality between their dexmedetomidine and comparator groups. Although they found significant differences in enzyme concentrations between their lignocaine-dexmedetomidine and control groups, Kim *et al.* (178) found no translation into clinical benefit: postoperative length of hospital stay; complications; 1-year mortality rates.

The results of this current study are similar to the results of Talke *et al.* (164), in their high-risk vascular patients, where they found no difference in mortality between the dexmedetomidine and placebo groups. They had a very low 30-day mortality (3/90 patients)

in their study; similar to this current study. Although underpowered to make conclusive assumptions, a meta-analysis by Biccard *et al.* (10), a subanalysis on mortality outcomes showed no significant difference between the dexmedetomidine and placebo groups.

On the contrary, Ji *et al.* (14) reported an association with significant reduction in in-hospital, 30-day and 1-year mortality rates in CABG patients who received dexmedetomidine. The shortcoming of their study was the heterogeneity of the participant groups. Of note was that at baseline, the patients had differences in factors that individually are known to be associated with increases in morbidity and mortality (185, 187, 229).

This sentiment about Ji *et al.* (14) is shared by Xue *et al.* (245) who, in a letter to the editor of a journal, also voiced these concerns. They pointed out the significant differences in preoperative and perioperative characteristics of the two groups (245). A similar issue was observed in a study by Brandao *et al.* (243) where a significant reduction in 30-day mortality was seen in the dexmedetomidine group. Their control group had significantly longer CPB time, higher Euro-score, older age and longer ICU stay. These factors have been shown to be associated with increases in morbidity and mortality (246, 247).

Neither did a meta-analysis by Wijeysundera *et al.* (124) find a significant reduction in mortality with other α-2 agonists. The evidence, therefore, of reduced short-term mortality when dexmedetomidine is used perioperatively, is poor and unreliable. This current study, with the concession that it's underpowered, gives a signal which is in agreement with the studies that have reported lack of benefit in this regard.

4.3.6 Dexmedetomidine and adverse outcomes

In total, 6 of our 90 patients had intra-aortic balloon pump (IABP) support in the perioperative period and 4 of these were in the dexmedetomidine group. One patient in the placebo group was supported with an extracorporeal membrane oxygenator (ECMO) device. The difference was not statistically significant ($p = 0.398$). The reported adverse events excluding those of low cardiac output were bleeding, wound sepsis and neurological fallout. The difference in

the total rate of adverse events (17% vs 9%) between the dexmedetomidine and placebo groups, respectively, was not statistically significant (p = 0.701).

Wagner *et al.* (248) conducted a literature review to define the multisystem adverse events of perioperative dexmedetomidine use. Outside of the known haemodynamic effects, they found no reports of other systemic events. Jones *et al.* (225) showed that increasing the dose of dexmedetomidine to above 0.7 μg/kg/h did not increase the risk of adverse events nor lead to improvement in sedation scores. This current study, similar to the literature on this subject, did not find a relationship between dexmedetomidine administration and kidney injury.

4.4 Conclusions and recommendations

Although not a subject of analysis in this current study, the evidence from clinical trials show a significant reduction in noradrenaline associated with dexmedetomidine. There is also evidence showing the maintenance of good haemodynamic conditions due to dexmedetomidine during cardiac surgery (99, 249). The evidence for attenuation of ischaemic markers in CABG surgery is, however, inconclusive.

Of concern is the issue of coronary vasoconstriction. Although this is postulated to confer preconditioning, methods of administration of dexmedetomidine in cardiac surgery differ. Administration time from induction through to aortic cross-clamping during vessel-harvesting can range from 30 to 120 minutes. This scenario means continuous vasoconstriction for prolonged periods in already diseased coronary vessels and a myocardium that is already compromised. This is in contrast to the initial preclinical studies that first alluded to the benefit of preconditioning (161). They induced this vasoconstriction in a controlled manner, at 25 to 30-minute periods with subsequent reperfusion.

It is clear from RCTs that, even when some benefit in ischaemic markers was seen, it did not translate to better clinical outcomes. What this lengthy period of vasoconstriction means to the compromised myocardial needs to be investigated further. It is evident in the studies that found an attenuation of ischaemic markers perioperatively, that this did not translate to better

clinical outcomes (166, 170). This is evidenced by the lack of improvement in LOS in hospital and ICU, and reduced mortality. The limitation in these studies was that they were inadequately powered.

ICU studies have not provided answers either. Their comparison to placebo has often been accompanied by increased doses of morphine or morphine equivalents (234, 236). Studies that took these into consideration have not found an added advantage in LOS in ICU and hospital when using dexmedetomidine (226, 237). What has been evident, is the beneficial effect of using dexmedetomidine in reducing delirium and its consequences in postoperative ICU patients (237).

Dexmedetomidine has consistently been shown to slow the heart rate and lead to lower blood pressures intraoperatively (10, 124). The slow heart rate caused by dexmedetomidine, while maintaining the diameter of intracardiac and endocardial vessels, improves oxygen delivery to the heart (223).

The superiority of other cardioprotective agents such as lignocaine, ketamine and volatile agents in attenuation of ischaemic markers has been noted (145, 178, 181). The lack of benefit in outcomes with the introduction of morphine and dexamethasone is also evident (177, 180).

In anaesthesia practice, there is a concept called “multimodal analgesia”. Perhaps “multimodal cardioprotection” is the right way to approach myocardial protection, as no single drug has “magic drug” properties. Dexmedetomidine seemed to fare better in the company of other cardioprotective agents (178, 181).

In this current study, “unassisted” dexmedetomidine, similar to the study by Bulow *et al.* (106), did not show any benefit in attenuating the rise in biochemical markers. It was however, found to be associated with prolonged hospital stay in this current study. This prolongation in hospital stay is not explicable by other factors. The issue of its prolonged

context-sensitive half-life, and possible negative effect on TNF-α, could be some of the reasons that need further exploration as reflected in other studies (177, 188).

The conclusion is therefore that there was no evidence that "unassisted" dexmedetomidine confers cardioprotection in CABG surgery by attenuation of the increase in ischaemic markers. This is despite evidence from animal studies that showed a reduction in infarct size (161). This current study, and previous studies have been underpowered to determine the effects of dexmedetomidine on outcomes conclusively. The results therefore cannot be used to generalise as they are unreliable.

The current study used change in high sensitive biomarker (hs-cTnT) as a surrogate for myocardial protection. We were however not able to find a significant difference in this outcome. The difference in other length of hospitalisation should be interpreted with caution considering the small sample size. The major limitation of all work so far, including of trials reviewed in this thesis, is of inadequate power.

A meta-analysis could be one way of overcoming this limitation. Alternatively, a large multicentre RCT, looking at the effects of dexmedetomidine on outcomes in CABG, is warranted. This adequately powered trial should address, among others, the timing of drug administration, dosing regimen and type of support in CABG surgery may provide more conclusive answers.

4.5 Limitations

The small sample size was a limitation in analysing the data, this was exacerbated by financial constraints. ICU-related logistical problems also contributed in delayed surgical intervention and delayed transfer of patients to the receiving ward. Lack of a sedation-analgesic protocol also made it difficult to make a clearer assessment of possible confounding problems to the outcomes of the study.

Postoperative CRP and NT-proBNP could have been added in the investigation of this current study. As an inflammatory marker and a biomarker of cardiac function, these two seem to be gaining ground in trials that investigate multi-biomarker use as prognostication tools for postoperative outcomes (250). They could, however, not be evaluated due to budget constraints. The change in these markers over time would also have been of clinical value as is shown in the vascular literature (251). Drug concentration levels to investigate the mean level of drug between the two groups that could be associated with a difference in outcome are a factor that needs investigating. This too was limited by financial constraints.

CHAPTER 5 : CORRELATION BETWEEN DEXMEDETOMIDINE, BIOMARKERS AND CLINICAL VARIABLES

5.1 Introduction

In this chapter, a correlation analysis is used to assess possible relationships between dexmedetomidine and clinical biomarker variables and to describe the strength and direction thereof. Evidence is increasing in trials that investigate use of multi-biomarkers as prognostication tools for postoperative outcomes (250). This investigation is therefore important in further assessing the relationship between biomarkers, perioperative dexmedetomidine administration in cardiac surgery and clinical outcomes.

5.1.1 Relationship between variables

A Spearman pairwise correlation test was used to determine the relationship between variables (Table 5.1). The following variables had a statistically significant correlation:

5.1.1.1 Perioperative dexmedetomidine

Dexmedetomidine administration had a statistically significant correlation with length of hospitalisation, ($r = 0.2164$, $p = 0.0417$).

5.1.1.2 Length of hospitalisation

Hospital LOS had a positive correlation with adverse events ($r = 0.6549$, $p < 0.0001$).

5.1.1.3 ICU length of stay

ICU LOS had an overwhelmingly significant correlation with hospital LOS and adverse events, ($r = 0.6839$, $p < 0.0001$) and ($r = 0.4584$, $p < 0.0001$), respectively.

5.1.1.4 Aortic cross-clamp time

Aocx time had a statistically significant correlation with CPB time ($r = 0.8200$, $p < 0.0001$), ICU LOS ($r = 0.3320$, $p = 0.0014$), and adverse events ($r = 0.2822$, $p = 0.0071$).

5.1.1.5 Cardiopulmonary bypass time

CPB time had a strongly significant correlation with LOS ICU ($r = 0.3447$, $p = 0.0009$) and adverse events ($r = 0.2826$, $p = 0.0070$).

5.1.1.6 Hs-cTnT at 24 hours

Hs-cTnT at 24 hours had a significant relationship with hs-cTnT at induction (r = 0.2730, p = 0.0137), CPB time (r = 0.2468, p = 0.0264), ICU LOS (r= 0.2191, p = 0.0494), and adverse events (r = 0.2963, p = 0.0072).

Table 5.1: Correlation between dexmedetomidine administration, biomarkers and clinical variables

Variable	Spearman's rho N								
	AE	Hosp	ICU	CPB	Aocx	Trop 0	Trop 24	CRP	pro BNP
AE	1.0000 90								
Hosp	0.6549*** 89	1.0000 89							
ICU	0.4584* 90	0.6839*** 89	1.0000 90						
CPB	0.2826** 90	0.1301 89	0.3347*** 90	1.0000 90					
Aocx	0.2822** 90	0.1546 89	0.3320** 90	0.8200*** 90	1.0000 90				
Trop– 0	– 0.1275 81	– 0.1020 80	0.0182 81	– 0.0018 81	0.0108 81	1.0000 81			
Trop– 24	0.2963** 81	0.2963 80	0.0838* 81	0.2191 81	0.2468* 81	0.2730* 81	1.0000 81		
CRP	– 0.1406 81	0.0114 80	0.0226 81	– 0.0763 81	– 0.0045 81	0.2598* 81	0.0813 81	1.0000 81	
proBNP	0.0092 81	– 0.0310 80	– 0.1182 81	– 0.0305 81	– 0.0560 81	0.2234* 81	0.1019 81	0.1513 81	1.0000 81
Dex	– 0.1414 90	– 0.2164* 89	– 0.1029 90	– 0.0416 90	– 0.0633 90	0.0920 81	0.0132 81	– 0.0535 81	– 0.1765 81

AE – adverse events, Aocx – aortic cross-clamp time; CPB – cardiopulmonary bypass time, Trop-0 – troponin at baseline; Trop-24 – troponin at 24 hours post baseline, CRP – C-reactive protein;
NT-proBNP – N-terminal pro b-type natriuretic peptide; Dex – Dexmedetomidine; Hosp – hospital, ICU – intensive care unit; Aocx – aortic cross-clamp, *p < 0.05, **p < 0.01, ***p < 0.0001

5.1.1.7 CRP

CRP and hs-cTnT at baseline had a statistically significant relationship (r = 0.2598, p = 0.0191).

5.1.1.8 NT-proBNP

NT-proBNP and hs-cTnT at baseline had a significant correlation (r = 0.2234, p = 0.0450).

5.2 Discussion

5.2.1 Dexmedetomidine

There was a statistically significant correlation between dexmedetomidine administration and LOS in hospital. A similar effect on ICU and hospital stay was found in a study by Patanwala *et al.* (193), with a significant increase in LOS in patients who received dexmedetomidine in ICU. Furthermore, they found an increase in hospital cost in the dexmedetomidine group when compared with propofol. Studies that found shorter LOS in ICU and hospital, often compared dexmedetomidine with long-acting sedatives in ICU (242). This was not the practice in the case of this current study.

The shortcoming in their study was its retrospective nature. Due to this, they could not account for any additional sedative used in ICU. There was also a possibility of selection bias in allocation of their patients as the baseline characteristics in their two groups were not similar. (193)

5.2.2 Preoperative hs-cTnT

There was a significant correlation between preoperative hs-cTnT, CRP and NT-proBNP. Troponin is a biomarker signalling myocardial injury. The cardiac troponin subunits are most commonly seen in myocardial infarction (45). CRP is an acute-phase protein which is an inflammatory marker in endothelial disease and atherogenesis (252). It also acts as a mediator in the inflammatory cascade (252). Increases in CRP were seen to correlate with infarct size in one study (253). NT-proBNP on the other hand, is an indicator of myocardial wall tension

and acts to modulate a multisystem response to cardiac failure and may also be secondary to ischaemia related myocardial stretch (254).

Toss *et al.* (255) found a significant correlation between CRP and cTnT levels. These three variables were looked at in studies that investigated a multiple biomarker system of risk stratification (253, 256, 257). NT-proBNP and hs-cTnI levels were seen to have a correlation with peak systolic strain and infarct size in a study by Smedsrud *et al.* (258). They used speckle tracking echocardiography and late-enhancement MRI to determine the strain pattern and infarct size.

Studies have shown a correlation between these variables (baseline hs-cTnT, 24-hour hs-cTnT, CRP and NT-proBNP), individually, with adverse outcome (255, 259-262). Liu *et al.* (263) showed that NT-proBNP was closely related to LOS in ICU and hospital. They found that the NT-proBNP cut-off of point of 2773.5 pg/ml was correlated with 30-day mortality.

Our study showed a significant correlation between these three variables. The difference in the variability of hs-cTnT can only be explained by 5%-changes in both CRP and NT-proBNP. Clinically, patients presenting for CABG surgery often have a history of chronic inflammatory processes evidenced by high CRP levels; myocardial ischaemia evidenced by elevated troponins; and cardiac failure evidenced by elevated NT-proBNP. The three variables signify potentially different but overlapping pathways in the pathophysiology of ischaemic heart disease and its associated cardiac failure.

5.2.3 24-hour hs-cTnT

A statistically significant correlation was found between 24-hour hs-cTnT and preoperative hs-cTnT, CPB time, ICU LOS and adverse events. Kocak *et al.* (196) found a correlation between postoperative hs-cTnT with Aocx and CPB time. The limitation of their study was a small sample size (n=17).

Similar to this current study, a correlation between peak cTn and CPB time, LOS in ICU and 30-day mortality was found in a study by Greenson *et al.* (111) which involved 71 CABG surgery patients. A relationship between preoperative cTn and adverse postoperative outcome has been shown in a study by Lyon *et al.* (261).

In a meta-analysis, Lurati Buse *et al.* (121) suggested that population types, cTn subunit types, cTn assays and timing of assays have an effect on cTn. They further suggested that these factors may be responsible for the difficulty in making definitive conclusions regarding postoperative cTn. (121)

5.2.4 Aortic cross-clamp time

This current study found a positive correlation between Aocx time with CPB time, LOS in ICU and adverse events. We included Aocx time into the total CPB time and this could be the reason for the very strong correlation between the CPB time and Aocx time. Furthermore, they often share the same causal factors (264). This relationship was shown in a study by Doenst *et* al (264), where an increase in CPB time was shown to increase with increasing Aocx time. Kocak *et al.* (196), also showed a correlation between Aocx time and CPB time. Their study however, was very small.

Michalopoulos *et al.* (229), in an analysis of 652 CABG surgery patients, found a similar significant correlation between Aocx time with LOS in ICU. Similarly, a study by Azarfarin *et al.* (265), also showed a relationship between CPB time, LOS in ICU and adverse events. Length of ventilation in ICU was also found to be correlated with Aocx time (186). The results of this current study are consistent with these findings.

5.2.5 Cardiopulmonary bypass time

A significant correlation between CPB time with LOS in ICU and rate of adverse events was shown in this current study. This is consistent with a previous study (265). In addition, a study by Salis *et al.* (185) found that CPB time was a risk factor for postoperative mortality.

5.2.6 ICU length of stay

In this current study, the length of stay in ICU showed a strong correlation with length of hospitalisation, and adverse events. The relationship between ICU and hospital LOS was the second strongest in the study, after that between CPB and Aocx time. Similar to the Aocx and CPB data, the total number of days in hospital included the number of days in ICU. This result shows that the increase in LOS in hospital rose in parallel with the increase in LOS in ICU.

There is often common causality between these two factors (241). A study by Kramer *et al.* (241) involving multiple ICUs, confirmed this point. They developed a model that tested the relationship between length of ICU and LOS in hospital in individual units. They found a correlation between ICU and hospital LOS in individual units when compared with each other. Al-Sarraf *et al.* (186) also found a correlation between ventilation time in ICU and LOS in hospital.

On the contrary, an analysis by Williams *et al.* (240, 266) found no relationship between ICU and hospital LOS. The limitation of their study was that they excluded those studies that would have made length of ICU stay an important factor in length of hospitalisation. They did, however, find an increase in LOS in ICU to be related to postoperative mortality.

5.2.7 Length of hospitalisation

The LOS in hospital was significantly related to the rate of adverse events in this current study. Forty-three per cent of the variance in length of hospitalisation could be explained by the rate of adverse events. Similar to this current study, Almashrafi *et al.* (267) found adverse events to be the most important determinant of postoperative LOS in ICU and hospital when compared with other factors.

5.3 Conclusions and recommendations

This current study found a correlation between dexmedetomidine administration and prolonged length of hospitalisation. The baseline characteristics of the study patients could

not explain this phenomenon. The context-sensitive half-life of dexmedetomidine compared with other drugs we used could have played a role in this effect. A similar effect was found by Patanwala *et al.* (193), and was a factor in those studies that compared dexmedetomidine with long-acting sedatives in the ICU setting (242).

The relationship between preoperative cardiac biomarker levels and outcome measures, have become a subject of investigations to stratify and prognosticate patients presenting for both major vascular and cardiac surgery. Their inclusion in newly developed risk stratification and multi-biomarker models is proof of this.

5.4 Limitations

There were no limitations in the investigation leading to the results of this chapter, however, a postoperative CRP and NT-proBNP were not tested due to financial constraints. These two biomarkers have been shown to be of value in the postoperative period and may have added value in the analysis.

CHAPTER 6 : DEXMEDETOMIDINE AS A PREDICTOR OF ADVERSE OUTCOME

6.1 Introduction

Previous results in the current study gave a signal of adverse outcome from perioperative dexmedetomidine administration in CABG surgery in the form of prolonged hospital stay. To further explore whether perioperative dexmedetomidine would predict prolonged length of stay in hospital, we used regression analysis to examine this relationship while controlling for other clinically relevant variables.

Eighty-one observations were included in the variables used in the regression analysis. Due to this factor, only five variables were included in each model. Variables CRP, NT-proBNP and hs-cTnT were not normally distributed and were therefore transformed.

Two simultaneous quantile regression models, for LOS in ICU and hospital were performed. The LOS in hospital included preoperative hs-cTnT in the first model (Model 1: hospital-stay) and the difference between preoperative and 24-hour hs-cTnT in the second (Model 2: hospital-stay). Thirty-day mortality was also assessed with 2 models. The independent variables: log of hs-cTnT; log of NT-proBNP; square of CRP; age; and ejection fraction were included in each model. These biochemical and clinical parameters were deemed important to include in the model as they have a potential to influence outcomes.

6.1.1 ICU stay as the outcome variable

Preoperative hs-cTnT in the first model (Model 1: ICU-stay) and the 24-hour hs-cTnT in the second (Model 2: ICU-stay), together with log of hs-cTnT, log of NT-proBNP, square of CRP, age, and ejection fraction, yielded the following results:

LOS in ICU

- There was strong evidence that a decrease in the log of preoperative NT-proBNP was a significant predictor of ICU stay when ICU stay was ≥ 4 days

(coefficient 0.45, SE 0.17, t 2.69, 95% CI 0.79 – – 0.12, p = 0.009)
(Model 1: ICU-stay) (Table 6.1).

- An increase in aortic cross-clamp time was a significant predictor of length of ICU stay when ICU stay was within 3–4 days
(coefficient 0.07, SE 0.01, t 2.20, 95% CI 0.002–0.0316, p = 0.031)
(Model 2: ICU-stay) (Table 6.2). The effect was very small.

6.1.2 Hospital stay as the outcome variable

The results of two simultaneous quantile regression models with relevant preoperative risk factors and preoperative hs-cTnT (Model 1: hospital-stay) (Table 6.3) are shown. The difference between preoperative and 24-hour hs-cTnT with relevant preoperative risk factors are in the second model (Model 2: hospital-stay) (Table 6.4).

LOS in hospital

- Age in years significantly predicted hospital stay in the first 0 to 7 days
(coefficient 0.08, SE 0.03, t 2.44, 95% CI 0.01–0.14, p = 0.017) when used in a model with preoperative independent variable, log of hs-cTnT
(Model 1: hospital stay) (Table 6.3).

- The log of 24-hour postoperative hs-cTnT had a significant effect in length of hospitalisation, when hospital stay was 0 to 7 days
(coefficient 0.5, SE 0.23, t 2.01, 95% CI 0.004–0.995, p = 0.048)
(Model 2: Hospital-stay) (Table 6.4).

- Drug (dexmedetomidine) administration also had a significant effect in hospital stay when hospital stay was within 0 to 7 days
(coefficient 0.8, SE 0.31, t 2.58, 95% CI 0.18–1.40, p = 0.012)
(Model 2: hospital-stay) (Table 6.4). This variable was the most significant in this model.

Table 6.1: Simultaneous quantile regression model for LOS in ICU – Model 1

Independent variable	Regression coefficient	T	p value	R^2
Intercept	4.0	2.4	0.022	0.02 (q25) (0–2 days)
Preoperative hs-cTnT log	0.1	0.33	0.743	
NT-proBNP log	–0.1	–0.28	0.780	
CRP square	0.0	0.02	0.980	
Age	–0.0	–1.14	0.257	
Intercept	4.9	2.97	0.004	0.03 (q50) (3–4 days)
Preoperative hs-cTnT log	0.1	0.42	0.673	
NT-proBNP log	–0.2	–0.98	0.331	
CRP square	0.3	1.17	0.241	
Age	–0.0	–0.95	0.344	
Intercept	6.0	2.40	0.019	0.04 (q75) (≥5 days)
Preoperative hs-cTnT log	0.2	0.41	0.685	
NT-proBNP log	–0.5	–2.69	0.009*	
CRP square	0.1	0.27	0.789	
Age	0.0	0.30	0.762	

(Model 1– ICU-stay) perioperative independent variables: hs-cTnT, high-sensitivity cardiac troponin; CRP, C-reactive protein; NT-proBNP, N-terminal pro b-type natriuretic peptide, (* $p < 0.05$)

Table 6.2: Simultaneous quantile regression model for LOS in ICU – Model 2

Independent variable	Regression coefficient	T	p value	R^2
Intercept	2.6	0.96	0.342	0.04 (q25) (0–2 days)
24-hour hs-cTnT log	0.1	0.45	0.655	
Aortic cross-clamp time	0.0	0.84	0.405	
Dexmedetomidine	0.2	0.65	0.515	
Age	–0.0	–1.10	0.274	
Intercept	1.1	0.33	0.740	0.05 (q50) (3–4 days)
24-hour hs-cTnT log	0.2	0.67	0.503	
Aortic cross-clamp time	0.07	2.20	0.031*	
Dexmedetomidine	0.3	0.62	0.540	
Age	–0.0	–0.63	0.533	
Intercept	0.6	0.01	0.990	0.07 (q75) (≥5 days)
24-hour hs-cTnT log	0.4	0.60	0.550	
Aortic cross-clamp time	0.0	0.15	0.073	
Dexmedetomidine	1.8	1.02	0.311	
Age	0.0	1.32	0.884	

(Model 2: ICU-stay) with perioperative independent variables: hs-cTnT, high-sensitivity cardiac troponin; CRP, C-reactive protein; NT-proBNP, N-terminal pro b-type natriuretic peptide, (* $p < 0.05$)

Table 6.3: Simultaneous quantile regression model for hospital stay – Model 1

Independent variable	Regression coefficient	T	p value	R^2
Intercept	2.1	0.81	0.419	0.03 (q25) (0–7 days)
Baseline hs-cTnT log	0.1	0.33	0.745	
NT-proBNP log	–0.0	–0.16	0.876	
CRP square	0.4	1.25	0.217	
Age	0.1	2.44	0.017*	
Intercept	6.8	1.94	0.057	0.02 (q50) (8–11 days)
Baseline hs-cTnT log	–0.1	–0.42	0.676	
NT-proBNP log	–0.3	–0.90	0.372	
CRP square	0.4	1.53	0.130	
Age	0.0	0.99	0.327	
Intercept	8.5	0.70	0.487	0.01 (q75) (≥12 days)
Baseline hs-cTnT log	–0.5	–0.92	0.360	
NT-proBNP log	–0.8	0.90	0.373	
CRP square	0.5	0.74	0.461	
Age	0.1	0.64	0.526	

(Model 1: hospital-stay) with preoperative independent variables (*$p < 0.05$): hs-cTnT – high-sensitivity cardiac troponin; CRP – C-reactive protein; NT-proBNP – N-terminal pro b-type natriuretic peptide

Table 6.4: Simultaneous quantile regression model for hospital stay – Model 2

Independent variable	Regression coefficient	T	p value	R^2
Intercept	1.33	0.69	0.494	0.04 (q25) (0–7 days)
24-hour hs-cTnT log	0.5	2.01	0.048*	
Aortic cross-clamp time	0.0	0.25	0.805	
Dexmedetomidine	0.8	2.58	0.012*	
Age	0.1	1.11	0.270	
Intercept	2.3	0.51	0.609	<0.01 (q50) (8–11 days)
24-hour hs-cTnT log	0.3	0.48	0.631	
Aortic cross-clamp time	0.0	0.46	0.646	
Dexmedetomidine	0.7	0.80	0.428	
Age	0.1	0.90	0.372	
Intercept	2.1	0.19	0.847	0.01 (q75) (≥12 days)
24-hour hs-cTnT log	–0.4	–0.25	0.805	
Aortic cross-clamp time	0.0	0.84	0.405	
Dexmedetomidine	1.1	0.86	0.394	
Age	0.1	1.32	0.189	

(Model 2: hospital stay) perioperative independent variables (*$p < 0.05$): hs-cTnT – high-sensitivity cardiac troponin; CRP – C-reactive protein; NT-proBNP – N-terminal pro b-type natriuretic peptide

6.1.3 Thirty-day mortality as an outcome variable

The exact logistic regression analysis model included the following preoperative independent variables: log of hs-cTnT at baseline; log of NT-proBNP; EF; and age (Model 1: 30-day mortality) (Table 6.5). The results are as follows:

30-day mortality

- The log of preoperative hs-cTnT was a significant independent predictor of 30-day mortality (OR 19.55, z 6.13, 95% CI 7.55–50.58, $p < 0.001$).

- The log of NT-proBNP was also revealed as an independent predictor of 30-day mortality (OR 0.14, z 3.08, 95% CI 0.04–0.49, $p = 0.002$).

- EF was a significant independent predictor of 30-day mortality (OR 1.45, z 5.35, 95% CI 1.26–1.66, $p < 0.001$).

- Age in years significantly predicted 30-day mortality (OR 1.46, z 3.18, 95%CI 1.16–1.85, $p = 0.001$).

Table 6.5: Exact logistic regression for 30-day mortality

Independent variable	Odds Ratio	z	p value	95% Confidence Interval
Intercept	7.06e– 22	–4.90	<0.001	2.43e–30 – 2.05e–13
Baseline hs-cTnT log	19.55	6.13	<0.001*	7.55–50.58
EF	1.45	5.35	<0.001*	1.26–1.66
NT-proBNP log	0.14	–3.08	0.002*	0.04–0.49
Age	1.46	3.18	0.001*	1.16–1.85

Postoperative independent variable hs-cTnT at baseline (pseudo $R^2 = 0.70$ F = 4)
(* $p < 0.05$) (Model 1: 30-day mortality); hs-cTnT – high-sensitivity cardiac troponin; NT-proBNP – N-terminal pro b-type natriuretic peptide

A second model, Model 2: 30-day mortality (Table 6.6), was tested to look at the association between dependant outcome variable, 30-day mortality with perioperative independent variables log of delta hs-cTnT; log of NT-proBNP; EF; and age. The results are as follows:

30-day mortality

- The log of the difference in hs-cTnT was a significant predictor of 30-day mortality (OR 8.92, z 2.54, 95% CI 1.65–48.27, p = 0.011).

- The log of NT-proBNP was a significant predictor of 30-day mortality (OR 0.26, z –3.79, 95% CI 0.13–0.53, p = 0.001).

- Age and EF did not reach statistical significance.

Table 6.6: Exact logistic regression for 30-day mortality

Independent variable	Odds Ratio	z	p value	95% Confidence Interval
Intercept	2.49e–23	3.27	0.001	6.86e–37 – 9.02e–10
Delta hs-cTnT log	8.92	2.54	0.011*	1.65–48.27
EF	1.19	1.29	0.196	0.91–1.54
NT-proBNP log	0.26	–3.79	<0.001*	0.13–0.53
Age	1.68	1.63	0.103	0.90–3.15

Delta hs-cTnT as an independent variable hs-cTnT (24 hours minus baseline) (Pseudo $R^2 = 0.45$ F= 4) (* $p < 0.05$) (Model 2: 30-day mortality); hs-cTnT – high-sensitivity cardiac troponin; NT-proBNP – N-terminal pro b-type natriuretic peptide

6.2 Discussion

6.2.1 Association between dexmedetomidine and outcome

Dexmedetomidine administration had a significant effect on hospital stay when hospital stay was from 0 to 7 days. This association was the strongest in this model. It is of importance to note that in this current study, the length of hospitalisation was inclusive of time spent in ICU. The minimum-maximum ICU LOS between the dexmedetomidine and placebo groups were 0 – 28 and 0 – 15 days, respectively.

In their retrospective study, Cheng *et al.* (188) found a significantly prolonged LOS in ICU in patients who received dexmedetomidine. No feasible explanation was found for this difference (188). Patanwala *et al.* (193) found a significant association between administration of dexmedetomidine with LOS in ICU and in hospital. In this current study this phenomenon was also found and may possibly be due to the prolonged dexmedetomidine context-sensitive half-life post infusion (250 min after an 8-hour infusion) (242). This, however, warrants further investigation.

6.2.2 Age as a predictor of outcome

A statistically significant association between age with length of hospitalisation (0–7 days), and 30-day mortality was found in this current study. The results are similar to those found by Wang *et al.* (268) in a study of octogenarians undergoing cardiac surgery. They found a higher adjusted postoperative ICU and hospital stay with older age. They also found increased 30-day mortality in older patients. We are not aware of any study that has found different results.

6.2.3 Ejection fraction as a predictor of outcome

Ejection fraction was a significant independent predictor of 1-month mortality. The model used could explain 70% of the variance in 30-day mortality. In addition to a finding on the association between age and outcome, Wang *et al.* (268) also found a low EF to be predictive of 30-day mortality. Although de Oliviera *et al.* (187) did not look at the association between EF and mortality, they found a significant association between length of hospitalisation with older age.

6.2.4 NT-proBNP as a predictor of outcome

The log of preoperative NT-proBNP was found to be an independent predictor of LOS in ICU when ICU stay was ≥ 4 days. It was also revealed as an independent predictor of 30-day mortality. Young *et al.* (195) found both preoperative and postoperative proBNP to be predictive of adverse outcome, however, they concluded that the postoperative proBNP levels had a higher predictive value than the preoperative proBNP levels. Barry *et al.* (269) found a rise in proBNP to be predictive of adverse events in their study, including rates of fatal MI.

In high-risk vascular patients, proBNP as a marker is gaining momentum as a significant predictor of adverse outcome. A meta-analysis by Biccard *et al.* (270) showed that proBNP had a higher predictive value than the traditional clinical risk factors. The evidence suggesting the significance of ProBNP has led to its inclusion in the new Canadian cardiac risk assessment guidelines (251).

6.2.5 Hs-cTnT as a predictor of outcome

The log of 24-hour postoperative hs-cTnT had a significant effect in length of hospitalisation, when hospital stay was 0–7 days. The log of preoperative hs-cTnT was also a significant independent factor of 30-day mortality. The log of the difference in hs-cTnT was a significant predictor of 30-day mortality.

Hs-cTnT, a marker of myocardial ischaemia, has been used extensively to assess outcome post cardiac surgery. Several studies have linked and found an association between cTn and adverse outcome, both in cardiac surgery and interventional cardiology (46, 47, 111, 114, 116, 197, 198, 271, 272). Lurati Buse *et al.* (121), in a meta-analysis, found an association between cTn and adverse cardiac outcome, mortality included. They suggested that; the assay type or subunit analysed; the timing of cTn testing; and the population tested, affected definitive conclusions on the predictive value of cTn (121). The results of this current study are in agreement with previous studies.

6.2.6 Aortic cross-clamp time as a predictor of outcome

In this current study, Aocx was predictive of LOS in ICU when ICU stay was within 3–4 days. Doenst *et al.* (264) found a significant association between Aocx and mortality. Similarly, Al Sarraf *et al.* (186) corroborated these results including those on the association between Aocx and ICU LOS. Aocx time is the period of ischaemia during which myocardial protection becomes cardinal to outcome.

Different strategies have been tested to determine the best method of protecting the heart during Aocx (44, 60). It would seem that operating on a beating heart far supersedes the method of using Aocx as Aocx time induces additional ischaemia-reperfusion damage to the heart (273). To be able to pick a single factor during this period of ischaemia-reperfusion as contributing to bad outcome would be difficult as many factors are at play. Research in this area still continues, and more can still be done.

6.3 Conclusions

This current study found perioperative administration of dexmedetomidine to be associated with prolonged hospital stay in the first 7 days of admission. The contribution of potential confounders in the drug regimen used in ICU, including morphine, has been considered. This current study did not, however, investigate the confounding effect of these drugs towards reported outcomes. The issue of the confounders, together with the long context-sensitive half-life of dexmedetomidine, may have contributed to the findings, as reported in previous ICU studies (234). Dexmedetomidine was also found in a study to significantly increase the levels of TNF-α (177, 188).

In this current study, preoperative hs-cTnT was shown to have the highest significance in predicting outcome, more than other preoperative variables, particularly with 30-day mortality. The log of NT-proBNP was also revealed as an independent predictor of 30-day mortality.

Compared with an assessment by Rodseth *et al.* (254), where they suggested that NT-proBNP had a higher predictive value than cTn in their vascular patients, we found troponin to be more predictive of mortality in our CABG surgery patient compared with NT-proBNP. Their target population was patients that needed risk stratification for vascular procedures, whereas CABG surgery patients are no longer an "at risk group" but rather have had an ischaemic cardiac event. Furthermore, this current study used a newer assay, hs-cTn, to predict outcome. Hs-cTn has been shown to be more sensitive than cTn (221). It is possible therefore that proBNP is far superior as a screening tool whereas cTn would predict adverse outcome in patients with confirmed myocardial ischaemia such as CABG surgery patients.

CRP, a marker of inflammation, was not seen as a predictor of adverse outcome in this current study. This finding in this current study is similar to other studies (253, 256, 257). A cost-analysis study to see the value of the biomarkers in predicting adverse outcome and reducing mortality and morbidity would be ideal. Moreover, these biomarkers have been investigated for development of multiple biomarker risk stratification in previous studies of at-risk patients (253, 256, 257).

6.4 Recommendations

A large multicentre study, ideally including patients operated on in the private sector, who may be receiving intervention much earlier in their disease process, is recommended to determine if the results of this study can be duplicated. The recommendations of the “Third Universal Definition of Myocardial Infarction" for use of troponin, electrocardiography, angiography and echocardiography in diagnosing perioperative MI should ideally be practiced by all cardiac units (57). A further investigation into the use of multiple biomarkers in outcome prediction in our population is encouraged. This might assist in patient stratification and resource allocation.

6.5 Limitations

The size of the sample precluded inclusion of more variables for testing for prediction of more outcome variables. To test for association with more variables, a larger sample size allowing for at least 15 observations per variable would be necessary.

CHAPTER 7 : ETHNICITY, GENDER, CORONARY ARTERY DISEASE AND RISK FACTORS

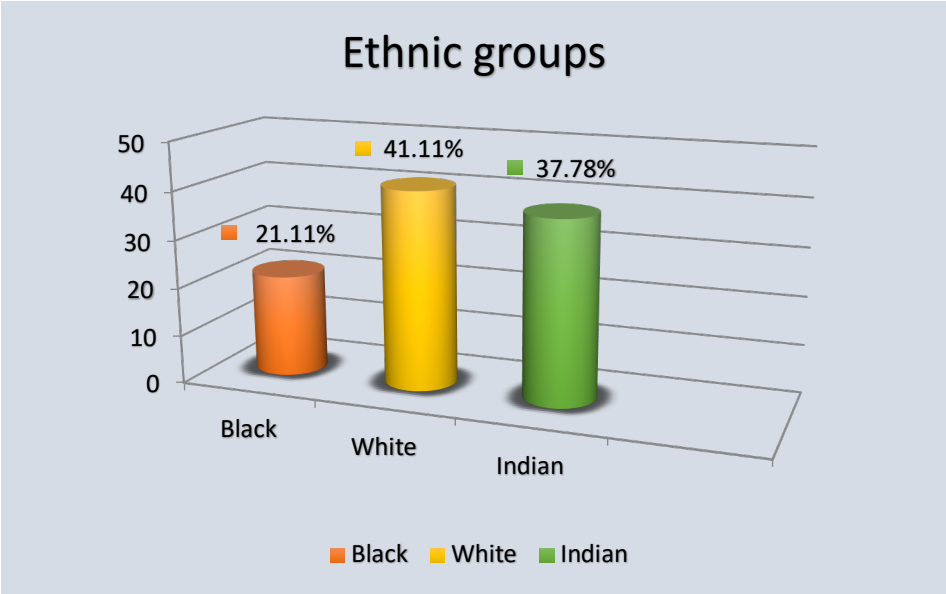
7.1 Introduction

Urbanisation and integration of society has led to changes in the prevalence of disease profiles between ethnic groups from what was traditionally understood. CAD among African patients is said to be increasing. Although there are epidemiological studies on the subject, we could not find those that compared disease burden between ethnic groups at presentation in the perioperative CABG surgery period. In this chapter, we present a risk factor profile of our study population in a perioperative CABG surgery period.

7.1.1 General Characteristics and Demographic Profile

The study was conducted at CMJAH, which is one of the 3 large teaching hospitals attached to the University of the Witwatersrand and the only one offering cardiothoracic surgical services for the indigent and poorer populations within the southern part of the province of Gauteng. Together, the three teaching hospitals serve all race groups, with CHBAH serving predominantly African patients, CMJAH a fair mix of Africans, whites, Indians and coloureds, and HJAH predominantly whites, Indians and coloureds. This is due to their geographical positions.

In a period of 29 months from February 2014 to June 2016, 95 patients (18 to 65 years old) with left main or triple vessel disease and presenting for CABG, were eligible to be included in the study. Three patients declined to participate in the study, and 90 consented to be part of the study and were enrolled into the study. The patients were grouped according to the ethnic group classification used in South Africa, and presented as Africans, Indians, whites and coloureds (271). Only one patient identified as coloured and thus for the purposes of analysis this patient was added to the Indian group. The proportions of the three groups were 41.1%, 37.8% and 21.1% whites, Indians and Africans, respectively (Figure 7.1). The female proportion among Indians, Africans and whites were 21%, 20% and 19%, respectively.

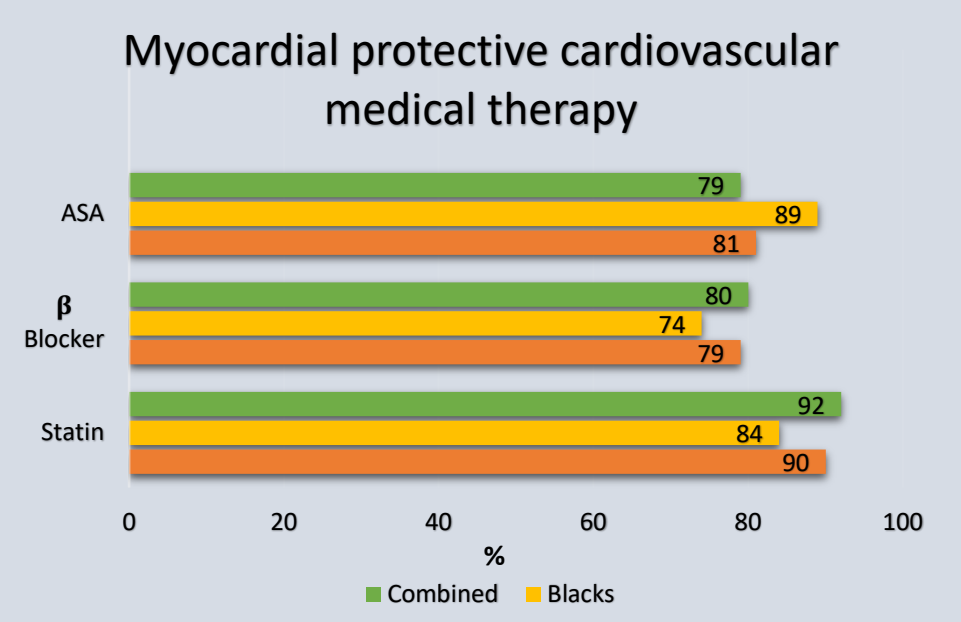


n = 90, data presented as percentage of total

Figure 7.1: Proportional representation of different ethnic groups

The median age of presentation was 57(51–60) years with the youngest patient presenting for CABG surgery 30 years old. Eighty per cent of these patients were male.

The history of cardiovascular medication, related to statins, beta blockers and aspirin, was taken. There was no difference in the proportions of patients on cardiovascular medical therapy between Africans and the combination of Indians and whites: acetylsalicylic acid (ASA) 89.47% vs. 78.87%, p = 0.294; statins 84.21% vs. 91.55%, p = 0.344; and β blockers 73.68% vs. 80.28%, p = 0.531), respectively (Figure 7.2). The mean number of coronary vessels grafted for the whole group was 2.92(0.706), with no difference in mean coronary vessels grafted between groups (p = 0.914) (Table 7.1).



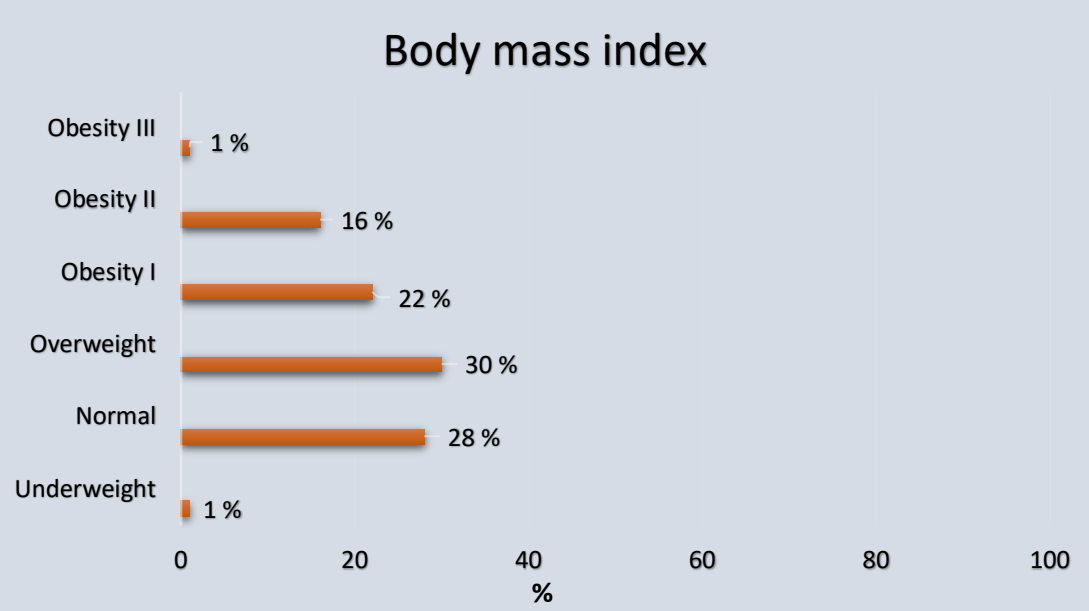
Proportions of patients on cardiovascular drugs, combined –the combined group includes whites and Asians, Total – the total sample of 90, ASA – aspirin

Figure 7.2: Comparison of proportions of patients on myocardial protective cardiovascular medical therapy by population group

Table 7.1: Classification of patients according to the WHO obesity and BMI classification

Classification	Obesity Class	BMI (kg/m^2)	n(%)
Underweight		<18.5	1(1)
Normal		18.5– 24.9	25(28)
Overweight		25– 29.9	27(30)
Obesity	I	30.0– 34.9	22(24)
	II	35.0– 39.9	14(16)
Extreme Obesity	III	≥40	1(1)

Adapted from the World Health Organisation (274). This table is copied in terms of Section 12 (Fair Dealing) of the SA Copyright Act No. 98 of 1978 (as amended).



Proportion of patients in each class: underweight (1%), normal weight (28%), overweight (30%), obesity class I (24%), obesity class II (16%), and extreme obesity class III (1%) for the whole group

Figure 7.3: Stratification of patients according to body mass index classification

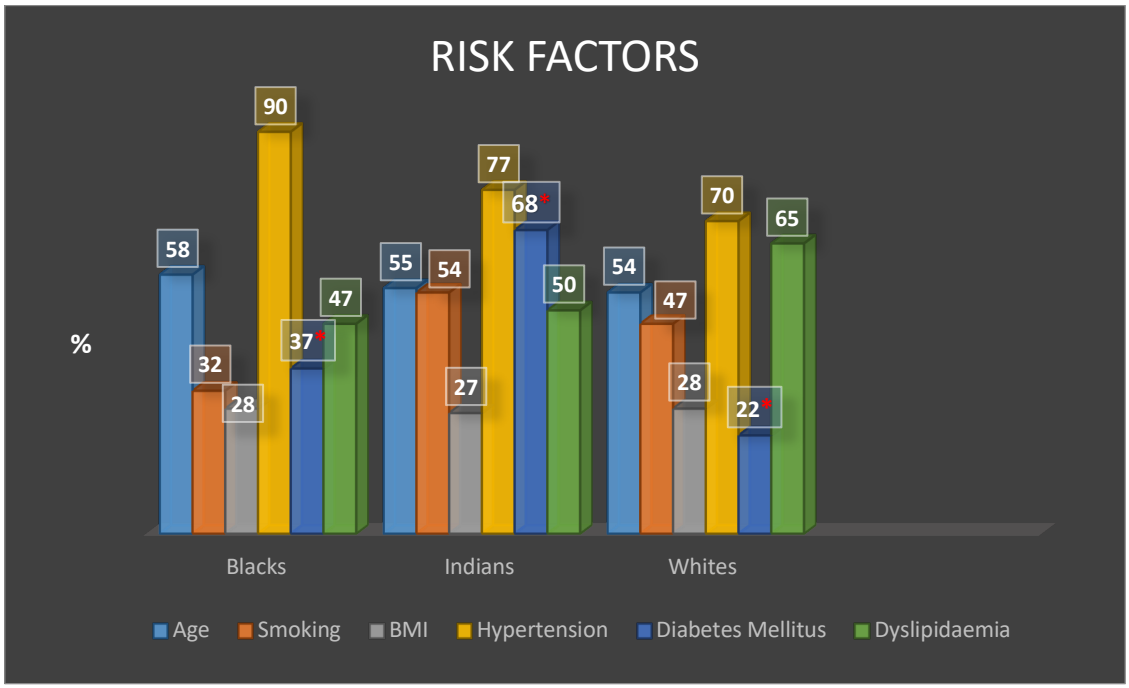
The median EF for the group was 53.5% (45–60), with the lowest recorded EF 20%. The New York Heart Association functional class for the three groups was comparable (Table 7.2).

7.1.2 Cardiovascular Risk Factors

The risk factor profile was obtained from history (self-reported) and assessed against the following modifiable risk factors: hypertension, diabetes mellitus, dyslipidaemia, smoking and obesity assessed as BMI (Table 7.1). For the whole group (n=90), the prevalence of hypertension was 76.7%; diabetes mellitus 42.2%; smoking 46.7%; and dyslipidaemia 55.6%. According to the BMI classification (Table 7.1), 71% of patients were either overweight or obese. The median (IQR) BMI for the whole group was 28(24–31) kg/m^2 with one patient presenting with a BMI of 55 kg/m^2. For the whole group, the following proportions for BMI were found: 1% underweight; 28% normal weight; 30% overweight; 24% obesity class I; 16% obesity class II; and 1% extreme obesity class III (Figure 7.3).

7.1.3 Ethnic and Gender Comparison

Compared with other ethnic groups, a significantly higher proportion of Indian 23(68%) patients presented with a history of diabetes mellitus vs. 7(37%) for Africans and 8(22%) for whites, $p < 0.001$ (Table 7.2). There was no statistically significant intergroup difference in the prevalence of other risk factors (Table 7.2). There were no differences in the total number of modifiable risk factors between Africans, whites and Indians 1.94(0.91), 2.02(0.79), 2.38(0.92), $p = 0.339$, respectively. There was no significant difference in BMI between Africans, whites and Indians 28.68(6.3) kg/m^2, 29.59(7.1) kg/m^2, and 28.02(6.5) kg/m^2, $p = 0.6453$, respectively.



Risk factor proportions as percentages of total per ethnic group; BMI – body mass index; x-axis – percentage of patients in the group Kruskal Wallis test: *p<0.05 for diabetes mellitus

Figure 7.4: A comparison of risk factor profiles by ethnic group

There was no statistical difference in the proportion of males to females in the different ethnic groups. Compared with whites and Indians, African patients had higher rates of hypertension (90%). A smaller proportion of Africans presented with a history of smoking (32%) compared with the other two ethnic groups (Table 7.2). White patients presented with higher rates of

dyslipidaemia (65%). However, the differences in these risk factors among the three ethnic groups did not reach statistical significance.

Table 7.2: A comparison of basic characteristics between three ethnic groups

Parameter	Africans (n=19)	Whites (n=37)	Indians (n=34)	p value
Female (%)	4(20)	7(19)	7(21)	0.977
Age (year) median(IQR)	60(53–62)	56(49–60)	56(51– 60)	0.186
NYHA mean(SD)	2.55(0.70)	2.59(0.94)	2.56(0.84)	0.253
*LVEF median(IQR)	50(45–55)	52(45–60)	55(45–60)	0.548
No. of vessels mean(SD)	2.94(0.70)	2.86(0.67)	2.97(0.67)	0.914
Smoking n(%)	6(32)	20(54)	16(47)	0.279
Hypertension n(%)	17(90)	26(70)	26(77)	0.274
Dyslipidaemia n(%)	9(47)	24(65)	17(50)	0.326
Diabetes Mellitus n(%)	7(37)	8(22)	23(68)	<0.001**
BMI median(IQR)	28(23–34)	28(24–33)	27(24–31)	0.645
RFS mean(SD)	1.94(0.91)	2.02(0.79)	2.38(0.92)	0.339
CPB time (min) median(IQR)	138(126–200)	152(130–170)	150(126–176)	0.966

RFS – total number of risk factors, BMI – body mass index, NYHA – New York heart association class, LVEF – left ventricular ejection fraction, *n=82, **$p < 0.001$

A comparison between African patients and a combined group of white and Indian patients showed no statistically significant difference in risk factor profile, number of risk factors and gender proportions (Table 7.3). The youngest patient (30 years old) in this current study was a white male patient with 3 risk factors and a strong family history of ischaemic heart disease (IHD). No other discernible difference in baseline characteristics and risk factor profile were found between these two groups (Table 7.3).

Table 7.3: A comparison of basic characteristics between Africans and a Combined group

Parameter	Africans (n=19)	Combined (n=71)	p value
Female n(%)	4(21.05)	14(19.72)	0.897
Age (yr) median(IQR)	60(53–62)	56(49–60)	0.075
BMI (kg/m^2) median(IQR)	28(23–34)	27(24–31)	0.824
Smoking n(%)	6(32)	36(51)	0.138
Dyslipidaemia n(%)	9(48)	41(58)	0.419
Hypertension n(%)	17(90)	52(73)	0.137
Diabetes Mellitus n(%)	7(37)	31(44)	0.593
RFS mean(SD)	1.94(0.20)	2.19(0.10)	0.275
EF% median(IQR)	50(45–55)	55(45–60)	0.302
CPB time (min) median(IQR)	138(126–200)	150(129–176)	0.902

RFS – total number of risk factors, BMI – body mass index, Combined – combined group of whites and Indians

Tables 7.4 and 7.5 show a comparison is made of biomarker profiles amongst the three ethnic groups. Although African patients had higher NT-proBNP, CRP and hs-cTnT levels at baseline, there was no statistical significance. African patients also had higher levels of postoperative hs-cTnT and IL-10 than the other two ethnic groups which also did not reach statistical significance (Table 7.5).

Table 7.4: A comparison of biomarker profiles between three ethnic groups

Parameter median(IQR)	Africans (n=15)	Whites (n=35)	Indians (n=31)	p value
Baseline NT-proBNP ng/L	359(129– 839)	344(126– 815)	171(61– 467)	0.233
Baseline CRP (ng/L)	6(1–13)	3(0–16)	2(1–6)	0.185
Baseline hs-cTnT (ng/L)	61(10–98)	12(8–33)	12(7–30)	0.264
Postoperative IL-6 (pg/ml)	0.075(0.03–0.1)	0.105(0.07– 0.19)	0.095(0.05–0.16)	0.355
Postoperative IL-10 (pg/ml)	4.45(4.14–8.52)	3.55(1.69–9.48)	4.72(3.2–5.36)	0.650
Postoperative hs-cTnT (ng/L)	451(296–1020)	363(223–721)	358(250–587)	0.268

hs-cTnT – high-sensitivity cardiac troponin, CRP – C-reactive protein, NT-proBNP – N-terminal pro b-type natriuretic peptide

Table 7.5: A comparison of biomarker profiles between Africans and the Combined group

Parameter median(IQR)	Africans (n=15)	Combined (n=66)	p value
Baseline NT-proBNP (ng/L)	359(129–839)	205(122–636)	0.310
Baseline CRP (ng/L)	6(1–13)	2(1–7)	0.153
Baseline hs-cTnT (ng/L)	61(10–98)	12(8–30)	0.103
Postoperative hs-cTnT (ng/L)	451(296–1020)	360.2(242–658)	0.111
Postoperative IL-6 (pg/ml)	0.075(0.03–0.1)	0.1(0.06–0.18)	0.171
Postoperative IL-10 (pg/ml)	4.45(4.14–8.52)	4.39(2.09–7.52)	0.788

hs-cTnT – high-sensitivity cardiac troponin, CRP – C-reactive protein, NT-proBNP – N-terminal pro b-type natriuretic peptide

Table 7.6 shows a comparison of baseline characteristics is made between males and females. It showed a statistically significantly higher proportion of smoking history in males compared with females (53% vs. 22% respectively, p = 0.02). Furthermore, a statistically significant higher proportion of females presented with a history of dyslipidaemia compared with males (78% vs. 50%, p = 0.034 respectively). There were no other significant differences in risk factor and baseline characteristics between males and females.

Table 7.6 A comparison of basic characteristic differences between males and females

Parameter	Male (n=72)	Female (n=18)	p value
Age (years) median(IQR)	56(50.5–60)	60(51–62)	0.171
NYHA mean(SD)	2.56(0.90)	2.58(0.61)	0.935
EF% median(IQR)	53(45–60)	55(45–62)	0.494
No. of vessels mean(SD)	2.93(0.67)	2.88(0.83)	0.824
Smoking n(%)	38(53)	4(22)	0.020*
Dyslipidaemia n(%)	36(50)	14(78)	0.034*
Hypertension n(%)	53(74)	16(89)	0.170
Diabetes Mellitus n(%)	28(39)	10(56)	0.200
BMI (kg/m^2) median(IQR)	27(24–31)	30.5(26–35)	0.189
RFS mean(SD)	2.11(0.10)	2.27(0.17)	0.476

LVEF – left ventricular ejection fraction; BMI – body mass index; RFS – number of risk factors; NYHA – New York heart association functional class, *$p < 0.05$

7.2 Discussion

7.2.1 Ethnicity and coronary artery disease

Ethnicity has been shown to play an important part in the occurrence of risk factors and their subsequent impact on prevalence of CAD (203, 208). Ethnicity has also been seen as a factor in clinical features and manifestations of disease processes (208).
An example of this can be seen in the varying complications of hypertension when African patients were compared with white patients (208). African hypertensive patients were found to have a higher incidence of renal dysfunction, stroke and CCF complications when compared with white patients, who in turn presented with a higher prevalence of CAD associated with their hypertension (208). Ethnicity has further been found to have an impact on variability in drug responses, particularly vasoactive agents (213, 275).

This current study found that 21.1% of patients who presented for CABG were Africans. A statistically significantly higher proportion of patients of Indian descent were found to have diabetes mellitus when compared with other groups. A statistically significant higher proportion of males were found to be smokers. When compared with males, a statistically significant higher proportion of females presented with dyslipidaemia.

Earlier studies that looked at CAD in South Africa showed a lower prevalence of CAD amongst African patients (22, 23). The situation was believed to be the same for Africans from Sub-Saharan regions of the African continent until the late 1990s (24). Whilst the incidence and disease pattern in Europeans and Asians in Southern Africa mirrored those of the international communities, the disease was found to be very rare in Africans in the 1970s (22). Albert (276) suggested in 2008 that changes in the prevalence of heart disease in urban Soweto's 1.1 million Africans, representing the largest African community in the Sub-Saharan region, might be due to "epidemiological transition".

Thus far, no study has looked at the basic characteristics and risk factor profile of patients presenting for CABG surgery in South Africa. Previous studies have, however, looked at these differences in nonsurgical communities (237, 241). Due to the previous spatial

distribution of the population, there was some skewness in comparison/representation of the ethnic groups in studies. Prior to1994, representation of ethnic groups at South African hospitals was also skewed. Reports of CAD in African patients in South Africa in the middle of the 20th century were predominantly from autopsy results (84, 86).

Seftel *et al.* (84) found only 30 African patients who had proven MI in a sample from the Old Johannesburg General Hospital in Hillbrow. The sample covered the period 1951–1961. Fifteen of these cases of MI were proven at post-mortem. At Baragwanath Hospital in Soweto, Schwartz *et al.* (85) reported a prevalence of CAD of 0.1%, while Schrire *et al.* (88) found a prevalence of 1.4% in Cape Town. A study by Chesler *et al.* (277) also reported 8 positive angiograms performed in African patients out of 800 in a 10-year period; in an area reported to have had over 1 million Africans.

Joubert *et al.* (87), using a convenience sampling method in patients who presented at a stroke clinic, found evidence of MI in 2.1% of patients. Research by Nethononda *et al.* (26), the Heart of Soweto (278) and INTERHEART studies (89) was conducted in predominantly African communities. To date, no study has looked at biomarkers and CABG outcomes amongst the different ethnic groups in the South African population.

In contrast to data from Nethononda *et al.* (26), this current study found no statistically significant difference in the prevalence of hypertension, dyslipidaemia and smoking when comparing African, white and Indian ethnic groups, respectively. Diabetes mellitus was found to be significantly higher in Indians when compared with African and white patients.

In a review by Akinboboye *et al.* (24), the prevalence of CAD was found to range from 0.01% to 2.4 % between the years 1951 and 1986, confirming the reported low prevalence of CAD disease in the East, West and Central African countries. Most of these cases were from autopsy studies as there were little reliable epidemiological data from most African countries.

Furthermore, Akinboboye *et al.* (24) showed that in their study Asian communities had the highest prevalence of CAD – similar to that in western countries. They also reported a prevalence of hypertension as high as 70% in one study in Zaire. They concluded that hypertension was associated with urbanization as compared with a previous theory that it was due to genetic maladaptation in those who were born in areas that produce little salt.

The small sample size in this current study is a significant limitation and the findings can only be hypothesis-generating for future large prospective studies to carefully look at differences in access to and outcome of CABG surgery among different population groups in South Africa and sub-Saharan Africa.

7.2.2 Risk factor profile

Cardiovascular risk factors and the coronary artery disease profile among the different ethnic groups in South Africa have also been investigated.

7.2.2.1 Hypertension

In 1983, Seedat *et al.* (205) found the prevalence of hypertension to be 25% in urban Zulus compared with 17.2% and 14% in white and Indian populations respectively. Despite these figures, CAD in Africans was found to be lower than in other ethnic groups. In 1994, Seedat *et al.* (86) found that smoking, hypercholesterolemia and hypertension were major risk factors in whites. They found hypertension, smoking and obesity in female patients to be the important risk factors in the cohort, however, they did not indicate whether there were differences between African, white and Indian women.

In this current study, the prevalence of hypertension in African patients was found to be as high as 90%, consistent with findings from a previous study (279). The difference between this group other ethnic groups was, however, not statistically significant. The Heart of Soweto study (91), similar to our study, did not find a statistically significant difference in the prevalence of hypertension in Africans when compared with other races. Isles *et al.* (206), comparing age and sex specific rates of death from CVD, using census data, found that

although more Africans had a high prevalence of hypertension, it was not commonly associated with CAD, but rather with cerebrovascular disease.

It has previously been suggested that, although African patients have a high prevalence of hypertension, their cardiovascular disease manifestation is with hypertensive heart disease, strokes and renal complications (207), compared with other ethnic groups. It was speculated that the high fibrinolytic activity among Africans was a contributing factor to a lower prevalence of CAD (24, 208). However, this is changing, possibly as a result of the epidemiological transition. The burden of CAD in African patients in this current study seemed higher, with hypertension as their principal risk factor. However, no conclusions can be drawn due to the small sample size.

7.2.2.2 Obesity

In 1992, a South African study by Seedat *et al.* (86) found 22.6% of African females to be obese when compared with males. An earlier study by the same group reported a total prevalence of obesity of 35.7% (280) in Africans. Tibazarwa *et al.* (91) found the rate of obesity to be 43% in African patients in Soweto, but this difference was not statistically significant when compared with other ethnic groups.

An American study found that more African-Americans presented with obesity than white patients (281). Obesity in that study was, however, associated with significantly less CAD in both races (281). In the Heart of Soweto study (91), with 88% of the patients being African, the rate of obesity was similar to other ethnic groups. Furthermore, the study found a statistically significantly higher proportion of females to be obese.

In this current study, 41% (37/90) of patients were found to be obese. However, there were no statistically significant differences between ethnic and gender groups. We attribute this to the relatively small numbers of African patients (19/90), particularly women. Indeed, out of the only four African women in the study, three (75%) were obese with BMI ≥ 28 kg/m^2.

7.2.2.3 Dyslipidaemia

In this current study, more whites reported a history of dyslipidaemia compared with the other two ethnic groups, although this difference did not reach statistical significance, possibly due to the small sample size. This finding is, however, consistent with a previous study by Seedat *et al.* (205). We found a high prevalence of dyslipidaemia among females compared with males and it was statistically significant. This was consistent with results of a study by Alberts *et al.* (29) among rural Africans from Limpopo, a province in South Africa. The challenge with our study was that we only had a small number of African women.

In the INTERHEART studies (89), Africans were found to have lower lipid levels than other ethnic groups and lower levels than the overall INTERHEART cohort (89). A gender-based analysis was not undertaken in that study.

7.2.2.4 Diabetes mellitus

This current study has found a prevalence of diabetes mellitus in Indian patients (68%) to be significantly higher when compared with African and white patients. African patients had the second highest prevalence of diabetes mellitus (37%), while white patients had the lowest (22%). This differs from a previous study by Omar *et al.* (282) that reported the prevalence of diabetes mellitus among Zulu patients in Natal to be much lower (4.2%). The higher prevalence of diabetes mellitus among African patients in this current study is similar to that reported in the Heart of SOWETO study (91).

7.2.2.5 Smoking

Although more than half of the Indian and white patients had a history of smoking, in this current study, compared with 37% smokers in African patients, the difference did not reach statistical significance.

A significantly higher proportion of other race groups were found to be presenting with a higher history of smoking when compared with African patients in the Heart of SOWETO study (91). In the INTERHEART study however, Africans had a similar prevalence of

smoking to other groups (89). Vorster *et al.* (27) found a smoking prevalence of 28% in their African participants, which was only higher than that found in Indian participants. A significantly higher rate of smoking in males than in females was found in our study. In Nigeria in 1976, smoking in secondary school students was found to be 13.6% in males compared with 10.3% in females.

7.2.2.6 Number of risk factors

We found no ethnic and gender disparity in the number of risk factors, with a mean of 2 risk factors per population group. This is in contrast to an earlier South African study by Seedat *et al.* (203) that showed that white patients commonly had an average of three risk factors whereas Africans had two. In that study, the common risk factors among whites were high cholesterol, smoking and hypertension. In both their study and this current study, smoking was shown to be an important risk factor among male patients. In this current study, in contrast to Seedat *et al.*'s study (203), dyslipidaemia, but not obesity was significantly higher among female patients.

In the Heart of SOWETO study (91), the prevalence of cardiovascular risk factors was found to be very high, with 59% of patients having multiple risk factors. In the same study, hypertension was found in 56% of patients of whom 44% were also obese. Only 13% of patients had no identifiable risk factors.

7.2.2.7 Age and gender

More males presented with CAD in this current study. The study did not find a significant difference in median age of presentation among different ethnic groups, nor were there any differences between genders. In contrast to this current study, the Heart of SOWETO study's population was in general younger, with women significantly younger than men at presentation (91).

7.3 Conclusions and recommendations

African patients seemed to present biochemically worse off than other ethnic groups, even though the differences in their biomarker levels did not reach statistical significance.

Postoperatively, their troponin levels were also higher than in other groups. They were also marginally older at presentation with a predominantly higher prevalence of hypertension compared with other groups. Their total number of risk factors was however lower than that in other ethnic groups.

The prevalence of CAD in African patients is rising. The increase has been postulated to be due to lifestyle changes that come with urbanisation and epidemiological transition. An integration of society can be seen, in that different ethnic groups are presenting with a similar prevalence of risk factors. The issue of obesity is no longer a female problem but is increasing among male patients.

Despite concerted efforts by the South African government to curb the increase in non-communicable diseases, the cardiovascular risk factors related to IHD are still rising. Salt intake in particular is seen as one of the major contributors to the risk of hypertension (283). It has now been legislated in South Africa that the mean population intake should be less than 5g/day by 2020 (283). All three ethnic groups have presented with high rates of hypertension – higher than their other risk factors.

7.4 Limitations

The patients enrolled in this current study were referrals from more than four surrounding hospitals to the cardiothoracic surgery unit. Long-term follow-up of these patients by physical means was difficult. Telephonic follow-up was possible in most cases but was also challenging. This limited their follow-up to a detailed history and not a clinical examination.

CHAPTER 8 : DEXMEDETOMIDINE PHARMACOETHNICITY

8.1 Introduction

Individualised medicine is an area that is growing rapidly, informed by ethnicity and genetics as factors leading to variability in response to drug therapy. It has been suggested that pharmacoethnicity, pharmacogenetics and pharmacogenomics are interlinked (93-95). The differences in ethnicity and genetics manifest themselves in variability of drug metabolism, transport proteins and drug target sites (93).

8.1.1 Baseline Characteristics

Data in this chapter is in the form of subgroups divided by intervention, ethnic group and outcome. The sample sizes are therefore small.

The results are presented as:

- a comparison between African patients and other ethnic groups in the dexmedetomidine group (Table 8.1)
- a comparison between African patients and other ethnic groups in the non-dexmedetomidine group (Table 8.2)
- a comparison between males and females in the dexmedetomidine group (Table 8.3).

At baseline, African patients presented with statistically significantly higher preoperative hs-cTnT levels when compared with the other group [Africans 61(11–70) ng/L and other 11(8–25) ng/L, p = 0.0259]. African patients also presented with a marginally higher preoperative NT-proBNP compared with the other group [Africans 531(359–3235) ng/L, other 198(126–567) ng/L, p = 0.0524]. All other baseline parameters were not significantly different.

Table 8.1: Dexmedetomidine group by ethnicity – baseline data

Parameter	Africans	n	Other or combined group	n	p value
NT-proBNP (ng/L) median(IQR)	531(359–3235)	7	198(126–567)	33	0.0524
CRP (ng/L) median(IQR)	7(4–13)	7	3(1–7)	33	0.1114
Hs-cTnT preoperative (ng/L) median(IQR)	61(11–70)	7	11(8–25)	33	0.0259*
LVEF (%) mean(SD)	48.56(12)	9	55.21(9.9)	33	0.1232
CPB time (min) median(IQR)	138(128–200)	9	133(152–178.5)	36	0.9096
Number of vessels mean(SD)	2.77(0.66)	9	2.97(0.67)	36	0.721

NT-proBNP – N-terminal pro b-type Natriuretic Peptide; CRP – C-reactive protein; CPB – cardiopulmonary bypass; LVEF – left ventricular ejection fraction; and delta hs-cTnT – difference between baseline and 24-hour hs-cTnT, *p < 0.05

Table 8.2: Non-dexmedetomidine group by ethnicity – baseline data

Parameter	Africans	n	Other or combined group	n	p value
NT-proBNP (ng/L) median(IQR)	180(106–340)	8	212(80–636)	33	0.6689
CRP (ng/L) median(IQR)	3.5(1–8)	8	2(1–6)	33	0.5256
Hs-cTnT preoperative (ng/L) median(IQR)	46(5.5–146.5)	8	12(8–31)	33	0.7172
LVEF (%) mean(SD)	49.7(9.9)	9	49.7(10.1)	31	0.9857
CPB time (min) median(IQR)	140(120–185)	10	150(124–170)	35	0.8914
Number of vessels mean(SD)	3.1(0.7)	10	2.85(0.77)	35	0.381

NT-proBNP – N-terminal pro b-type Natriuretic Peptide; CRP – C-reactive protein; CPB – cardiopulmonary bypass; LVEF – left ventricular ejection fraction; and delta hs-cTnT – difference between baseline and 24-hour hs-cTnT, *p < 0.05

Table 8.3: African patients by drug – baseline data

Parameter	Dexmedetomidine	n	Non-dexmedetomidine	n	p value
NT-proBNP (ng/L) median(IQR)	531(359–3235)	7	180(106–340)	8	0.0372*
CRP (ng/L) median(IQR)	7(4–13)	7	3.5(1–8)	8	0.1981
Hs-cTnT preoperative (ng/L) median(IQR)	61(11–70)	7	46(5.5–146.5)	8	0.9538
LVEF (%) mean(SD)	48.56(12)	9	49.7(9.9)	9	0.8166
CPB time (min) median(IQR)	138(128–200)	9	140(120–185)	10	0.8380
Number of vessels mean(SD)	2.77(0.66)	9	3.1(0.7)	10	0.334

NT-proBNP, N-terminal pro b-type Natriuretic Peptide; CRP, C-reactive protein, CPB – cardiopulmonary bypass; LVEF, left ventricular ejection fraction; delta hs-cTnT, difference between baseline and 24-hour hs-cTnT, *$p < 0.05$

There were no statistical differences in the baseline characteristics between ethnic groups in the non-dexmedetomidine group (Table 8.2). African patients in the dexmedetomidine group presented with statistically significantly higher NT-proBNP levels at baseline than African patients in the non-dexmedetomidine group (Table 8.3). There was no difference in the preoperative baseline characteristics between males and females in the dexmedetomidine group (Table 8.4).

Table 8.4: Dexmedetomidine group by gender – baseline data

Parameter	Male	n	Female	n	p value
Hs-cTnT preoperative (ng/L) median(IQR)	13(8–35)	30	12.5(9–23)	10	0.6279
NT-proBNP (ng/L) median(IQR)	234(137–724)	30	411(122–824)	10	0.6017
CRP (ng/L) median(IQR)	4(2–13)	30	1.5(1–6)	10	0.3387
LVEF (%) mean(SD)	53.45(10.9)	31	54.72(9.9)	11	0.7353
CPB time (min) median(IQR)	150(130–175)	34	176(129–185)	11	0.4052
Number of vessels mean(SD)	2.9(0.59)	34	3.1(0.83)	11	0.133

NT-proBNP – N-terminal pro b-type Natriuretic Peptide; CRP – C-reactive protein; CPB – cardiopulmonary bypass; LVEF – left ventricular ejection fraction; delta hs-cTnT – difference between baseline and 24-hour hs-cTnT

8.1.2 Postoperative ethnic and gender comparisons

Table 8.5 shows a comparison of postoperative parameters between Africans and the combined group of other ethnic groups among patients who received dexmedetomidine. There were no differences in postoperative ischaemic and inflammatory biomarkers between groups. This is despite the fact that African patients in the dexmedetomidine group presented with worse preoperative biomarker profiles than the combined group.

The postoperative parameters between ethnic groups in the non-dexmedetomidine group showed no statistical difference (Table 8.6). In comparison, African patients in the dexmedetomidine group presented with significantly higher NT-proBNP levels at baseline than African patients in the non-dexmedetomidine group (Table 8.7). Dexmedetomidine administration did not lead to differences in either biomarker or clinical outcomes when the dexmedetomidine group was analysed according to gender (Table 8.8).

Table 8.5: Dexmedetomidine group by ethnicity – postoperative data

Parameter	African	n	Other	n	p value
Hs-cTnT 24-hr (ng/L) median(IQR)	451(295–927))	7	363(264–625)	33	0.4765
Delta hs-cTnT (ng/L) median(IQR)	427(232–793)	7	350(231–586)	33	0.5333
IL-10 (pg/ml) median(IQR)	4.23(4.14–4.45)	6	4.72(2.38–9.76)	20	0.7339
IL-6 (pg/ml) median(IQR)	0.07(0.02–0.15)	9	0.09(0.06–0.19)	36	0.2402
ICU LOS (days) median(IQR)	3(3–4)	9	3.5(2–4.5)	36	0.8729
Hospital LOS (days) median(IQR)	8(7–14)	9	8.5(7–11)	36	0.7966
Adverse Events (%) mean(SD)	1.11(0.33)	9	1.16(0.38)	36	0.684

IL – interleukin; LOS, length of stay; ICU – intensive care unit; and delta hs-cTnT – difference between baseline and 24-hour hs-cTnT

Table 8.6: Non-dexmedetomidine group by ethnicity – postoperative data

Parameter	African	n	Other	n	p value
Hs-cTnT 24-hr (ng/L) median(IQR)	444.5(301.5–127.4)	8	336(242–691)	33	0.138
Delta hs-cTnT (ng/L) mean(SD)	345(243–1034)	8	276(215–627)	33	0.3744
IL-10 (pg/ml) median(IQR)	6.54(2.28–9.01)	6	3.89(1.69–5.35)	21	0.4657
IL-6 (pg/ml) median(IQR)	0.08(0.05–0.1)	7	0.1(0.06–0.17)	29	0.4342
ICU LOS (days) median(IQR)	2.5(2–5)	10	3(2–4)	35	0.9774
Hospital LOS (days) median(IQR)	8(7–10)	10	8(6–10)	35	0.4260
Adverse events (%) mean(SD)	1.2(0.42)	10	1.02(0.17	35	0.057

IL – interleukin; LOS – length of stay; ICU– intensive care unit; and delta hs-cTnT – difference between baseline and 24-hour hs-cTnT

Table 8.7: Postoperative parameters between dexmedetomidine and non-dexmedetomidine groups among African patients

Parameter	Dexmedetomidine	n	Non-dexmedetomidine	n	p value
Hs-cTnT 24-hr (ng/L) median(IQR)	451(295–927))	7	444.5(301.5–127.4)	8	0.4875
Delta hs-cTnT (ng/L) median(IQR)	427(232–793)	7	345(243–1034)	8	0.7721
IL-10 (pg/ml) median(IQR)	4.23(4.14–4.45)	6	6.54(2.28–9.01)	6	0.3580
IL-6 (pg/ml) median(IQR)	0.07(0.02–0.15)	9	0.08(0.05–0.1)	7	0.8978
ICU LOS (days) median(IQR)	3(3–4)	9	2.5(2–5)	10	0.8346
Hospital LOS (days) median(IQR)	8(7–14)	9	8(7–10)	10	0.5627
Adverse Events (%) mean(SD)	1.11(0.33)	9	1.2(0.42)	10	0.6196

IL – interleukin; LOS – length of stay; ICU – intensive care unit; and delta hs-cTnT – difference between baseline and 24-hour hs-cTnT

Table 8.8: Postoperative parameters in the dexmedetomidine group according to gender

Parameter	Male	n	Female	n	p value
IL-10 (pg/ml) median(IQR)	4.45(2.47–5.67)	17	4.30(3.38–9.76)	8	0.8156
IL-6 (pg/ml) median(IQR)	0.09(0.06–0.17)	25	0.09(0.07–0.11)	9	0.9220
Hs-cTnT 24-hr (ng/L) median(IQR)	362.5(264–625)	30	403.5(303–1020)	10	0.5118
Delta hs-cTnT (ng/L) median(IQR)	347(231–586)	30	377.5(288–950)	10	0.4725
ICU LOS (days)	3(2–5)	34	4(2–4)	11	0.9138
Hospital LOS (days)	8(7–11)	34	10(8–12)	11	0.4883
Adverse events (%) mean(SD)	1.11(0.33)	34	1.27(0.46)	11	0.227

IL – interleukin; LOS – length of stay; ICU – intensive care unit; and delta hs-cTnT – difference between baseline and 24-hour hs-cTnT

8.2 Discussion

Ethnicity as a factor in variability of response to drug therapy has been previously investigated (95). This has led to suggestions of individualised medicine (93, 284). Pharmacoethnicity, pharmacogenetics and pharmacogenomics have been shown to be interlinked (93-95). It has been suggested that the differences in ethnicity and genetics manifest themselves in variability of drug metabolism, transport proteins and drug target sites (93).

Our current study was not powered for an analysis on dexmedetomidine pharmacoethnicity. Like previous studies on the subject, our numbers were small given that this is a new field of study (209). Therefore, our results should be interpreted with caution and at best are hypothesis generating. Preoperative data in this current study show significantly higher levels of preoperative hs-cTnT in African patients when compared with other ethnic groups. Furthermore, the levels of NT-proBNP at baseline were marginally higher in African patients when compared with the other combined ethnic groups. However, there was no statistical difference in LVEF between these groups.

Despite the differences in preoperative biomarker values, there was no statistically significant difference in postoperative biomarker and clinical outcomes in patients who received dexmedetomidine when African patients were compared with the other ethnic groups combined. Importantly, despite presenting with significantly higher NT-proBNP levels, African patients in the dexmedetomidine group did not fare worse in the postoperative period when compared to African patients in the non-dexmedetomidine group. Furthermore, within the dexmedetomidine group, there were no differences in biomarker levels and clinical outcomes when patients were compared according to gender groups.

The effects of dexmedetomidine are mediated through α-2 adrenoceptors (82, 83). We found no studies in the English literature comparing biomarker differences between ethnic groups in association with dexmedetomidine. A previous study had shown the effects of clonidine on blood pressure reduction to be different between African and white patients (213). These results were not reproducible when the cardiovascular effects of dexmedetomidine were

tested and compared between ethnic groups (210). Of note is that the proportions of α-1 to α-2 receptor activity between dexmedetomidine and clonidine were different (210). Dexmedetomidine is a highly selective α-2 agonist similar to clonidine but with a greater affinity for the α-2 receptor. Clonidine has a specificity of 220:1 (α-2:α-1), whereas dexmedetomidine exhibits a specificity of 1620:1 (207).

Muszkat *et al.* (209), while testing vasoconstrictor effects of dexmedetomidine by infusing dexmedetomidine regionally, in the vessels of healthy volunteers, did not find any difference between African and white patients. They also found that gene polymorphism did not affect the veno-constrictor effects of dexmedetomidine. Yagar *et al.* (212), had however found a statistically significant dexmedetomidine-induced sedation score in patients with different gene alleles, which was not ethnicity related. In contrast, Tellor *et al*. (211) found non-African race to be an independently associated with failure of dexmedetomidine sedation.

This current study is the first to compare the impact of dexmedetomidine administration on perioperative biomarker levels as a surrogate to myocardial damage between different ethnic groups as well as the impact on clinical outcome measures such as length of ICU stay, length of hospitalisation and other adverse events. Although the study is limited by a small sample size, particularly a fewer number of African patients; a larger sample size may be able to show a significant difference between ethnic groups.

8.3 Limitations

Comparisons of the impact of dexmedetomidine on perioperative biomarkers and clinical outcome were limited by the small number of patients studied, particularly African patients. Therefore, the results of our study should be interpreted with caution and can at best only be hypothesis formulating and should be explored in a larger study.

CHAPTER 9 : THE INFLUENCE OF DEXMEDETOMIDINE ON TROPONIN CHANGES: A SYSTEMATIC REVIEW OF RANDOMISED CONTROLLED TRIALS

9.1 Introduction

Studies that investigated the effects of dexmedetomidine on changes in biomarker and clinical outcomes are few. Most of the studies published had small sample sizes. The meta-analyses that have reported on effects of dexmedetomidine on outcomes in cardiac surgery have been predominantly inclusive of postoperative sedation studies (238, 298-300).

Gong *et* al. (287), conducted the only meta-analysis of randomised controlled trials in the literature, which included only cardiac patients with predominantly paediatric cardiac patients. Their outcomes were however only haemodynamics parameters such as blood pressure and heart rate. It was found to be important therefore to conduct a systematic review and meta-analysis of randomised controlled trials that investigated the effects of intraoperative dexmedetomidine on changes in troponin, LOS, mortality, and changes in other biomarkers during cardiac surgery. A sub-analysis of the CABG group (off- and on-pump) is intended where feasible.

We used the population, intervention, comparison, outcome and study design (PICOS) model to conduct a systematic review to evaluate the impact of intraoperative dexmedetomidine compared to placebo or "other" therapy on outcomes in cardiac surgery. Randomised controlled clinical trials (RCTs) of patients undergoing cardiac surgery reporting at least one of the outcomes eligibly were included. A PubMed Central, Cochrane Library, ProQuest, Web Of Science and Scopus search was conducted by two investigators independently. The primary outcome was the impact of dexmedetomidine on change in troponin levels in ng/ml at 24 hours or on day-1 postsurgery. The secondary outcomes were the impact of dexmedetomidine on ProBNP, CKMB and inflammatory (IL-6, IL-8, IL-1, TNFα) biomarkers 24-hours postsurgery; length of stay in intensive care and hospitalisation, and motarlity [short term ($\leq$ 30days) and long term($\geq$ 30days)]. A quantitative synthesis of the data was conducted and analysed.

9.2 Background

Alpha-2 agonists are postulated to exert their cardioprotective effects by attenuating the release of catecholamines and inhibiting stress-induced tachycardia (49, 99, 124). Through their α-2A adrenergic and the imidazole-1 receptor mediated lowering of the central sympathetic tone, they induce analgesia, are sedative and have anxiolytic effects (77, 78). Major adverse cardiac events post cardiac surgery are emotionally devastating for the patient, the family and the medical team (50) and have dire financial consequences (51). Sympatho-modulatory therapies, including ß-adrenergic blockers, regional anaesthesia and α2-adrenergic agonists, are some of the modalities that were studied (65-68).

Dexmedetomidine administration in preclinical cardiac studies had shown some indication of myocardial protection (285, 286). Human perioperative cardiac surgical clinical studies have reported inconclusive evidence on myocardial protection in the use of dexmedetomidine (166, 177, 178, 180, 287). A meta-analysis by Geng *et al.* (239) that found significantly reduced length of ICU stay had included intensive care sedation studies and an intraoperative study with significant heterogeneity.

Gong *et al.* (299), in their review and meta-analysis of randomised controlled trials, included both paediatric and adult patients. Their outcomes of interest were haemodynamic parameters such as blood pressure and heart rate. We have not found a systematic review and meta-analysis of RCTs that reported on the effects of dexmedetomidine on troponin changes in cardiac surgery, compared to other therapy. No systematic review was found in the literature reporting on the effects of dexmedetomidine on troponin changes in CABG surgery.

We performed a meta-analysis of RCTs to evaluate its benefit on troponin changes and other outcomes in cardiac surgical cases [valve, on-pump coronary artery bypass graft (CABG), mini-cardiopulmonary bypass coronary artery bypass graft (mini-CPB CABG), and off-pump coronary artery bypass graft (OPCAB) surgery] where dexmedetomidine was used intraoperatively compared to other therapy.

9.3 Methods

Prospective, randomised controlled trials that reported the use of intra-operative dexmedetomidine in human adult cardiac surgery, compared with placebo or other therapy from the same population, were included. The trials included were in published literature with no language limitation, provided the authors could provide required data where ineligible. A discriminator for dexmedetomidine dose, type of comparator, timing of intraoperative commencement and discontinuation or combination with other therapy was not used.

9.3.1 Literature search

9.3.1.1 Search strategy and selection of studies

The Cochrane Library, Scopus and PubMed databases were searched systematically. The Major MeSH terms and important keywords used to conduct the initial basic search were: "dexmedetomidine", "cardiovascular surgical procedure", "surgical procedure, operative", "humans" and "adult". The following filters were used: "human", "01 Jan 2008 to April 2018", "+18years" and "randomised controlled trial". Reference lists of relevant literature, including reviews and meta-analyses, were further screened and studies of interest assessed for inclusion into the analysis. Studies included were: randomised controlled trials; cardiac surgical (valves, coronaries – both on- and off-pump, and other intra-cardiac procedures); adult (>18 years old); description of use of dexmedetomidine intra-operatively in cardiac surgery; and no language limitation. We retrieved studies from January 2008 to April 2018. The complete search strategy is presented in a PRISMA 2009 Flow Diagram format in Figure 9.1.

9.3.1.2 Data extraction and quality assessment

The titles and abstracts were scanned and full-text articles were independently retrieved by two reviewers. Relevant citations were selected and disputes were resolved by consensus. A third reviewer oversaw the process. We included published peer-reviewed articles. Authors of studies with unclear or incomplete data were contacted to request detailed data. Studies where complete data could not be found after an attempt to contact the authors were excluded.

Standardised data extraction and quality assessment sheets were used as follows: The data extraction sheets were in an Excel spreadsheet format and included the characteristics of the studies (main author and reference) and of patients enrolled including for both the dexmedetomidine and control group. For each trial, data on sample size, type of cardiac surgery, population demographics (age and gender), left ventricular ejection fraction (LVEF) (%), cardiopulmonary bypass (CPB) time (in minutes) were extracted and tabulated (Table 9.1).

Data on type of study (randomised controlled trial only were included for analysis), type of troponin assayed, and other cardiac biomarkers such as ProBNP and CKMB were collected. Data on inflammatory biomarkers such as IL-6, IL-8, IL-1 and TNFα were also tabled. Data were reported as mean/median and SD/IQR and measurement units where necessary (eg. ng/ml).

Statistical calculators were used to convert the entries into a single uniform representation [eg data presented as median (IQR) were converted to mean (SD)] using Stata/SE 13.1 statistical software (Copyright 1985–2013 Stata Corp LP Statistics/Data Analysis Stata Corp 4905 Lakeway Drive Special Edition College Station, Texas 77845 USA 800–STATA–PC http://www.stata.com, stata@stata.com and VassarStats: Website for Statistical Computation – http://www. http://vassarstats.net. Data were verified independently for accuracy and consistency of data entry.

Clinical outcomes were also charted on their separate sheet and included length of stay in ICU, length of hospitalization and mortality. Those that reported length of stay in days were separated from those reporting in hours. Mortality data was divided into short term (within 30 days) and long term. The different tables were imported into Review Manager 5.3 software (The Nordic Cochrane Centre, Copenhagen, Denmark) used for preparing and maintaining Cochrane Reviews. Review Manager facilitates preparation of protocols and full reviews, including text, characteristics of studies, comparison tables, and study data.

The Cochrane Risk of Bias Methods format was used for methodological quality assessment of trials to evaluate the quality of included trials (Table 9.2). The methods included: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other bias. A judgement of “high”, “low” or “unclear” risk of material bias was then made. Disagreements were resolved through discussion and a third reviewer was consulted if consensus was not reached.

Patients who received any dose of dexmedetomidine were treated as the dexmedetomidine group, and patients who received placebo/saline or any other therapy were treated as the control group. For a study with multiple groups, the dexmedetomidine groups and the comparator groups were combined to form a single dexmedetomidine and a single control group.

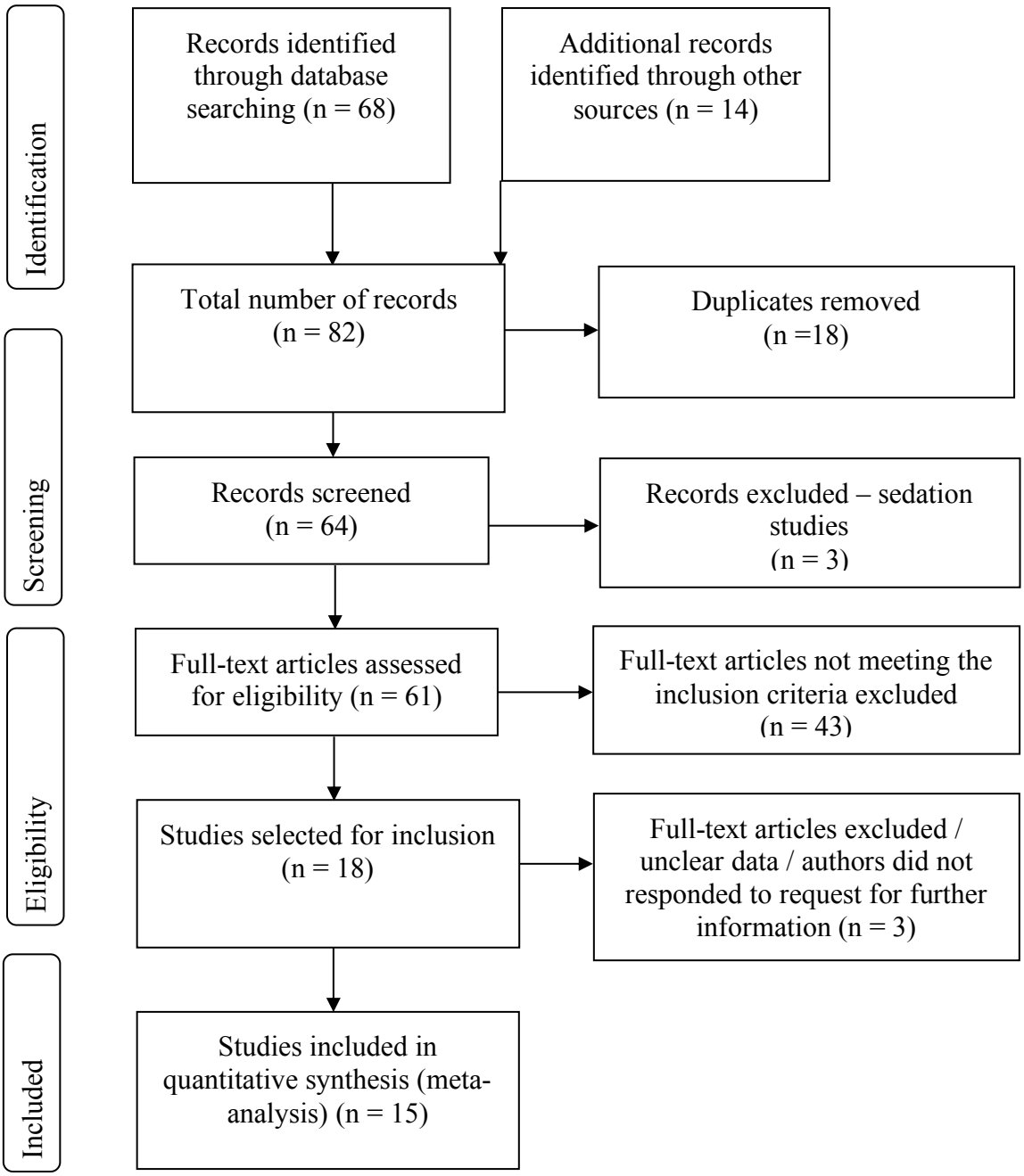


Figure 9.1: PRISMA 2009 flow diagram

9.3.2 Statistical analysis

Extracted data from included studies were used to calculate the mean differences / standardised mean differences for continuous outcomes, odds ratios for binary outcomes, 95% confidence intervals and two-sided p-values for each outcome. A p-value < 0.05 was considered statistically significant. The presence of statistical heterogeneity of outcomes across trials was assessed using the I^2 measure, and I^2>50% when p<0.10 indicated substantial heterogeneity.

Trials with significant heterogeneity were reported as standardised mean differences and those with insignificant heterogeneity as mean differences. Overall effects in studies with significant heterogeneity were reported as random effects and those with insignificant heterogeneity as fixed effects. Meta-analyses were performed with the assistance of a biostatistician using the RevMan 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) statistical software. Power analysis was performed using Stata/SE 13.1 statistical software (Copyright 1985–2013 Stata Corp LP Statistics/Data Analysis Stata Corp 4905 Lakeway Drive Special Edition College Station, Texas 77845 USA 800–STATA–PC http://www.stata.com, stata@stata.com).

9.3.3 Inclusion and exclusion criteria

The inclusion criteria of eligible studies were as follows:

1) prospective, randomised controlled trials published after 1 January, 2008;
2) studies of adult patients who underwent cardiac surgery;
3) use of intraoperative dexmedetomidine administration;
4) comparison of the effects of dexmedetomidine with placebo or other therapy; and
5) availability of detailed data.

The exclusion criteria were as follows

1) single-arm studies;
2) in vitro studies;
3) trials which did not report on any of the endpoints;
4) case reports; and
5) retrospective studies.

9.3.4 Primary and secondary data points

Primary endpoints

1) change in troponin levels in ng/ml at 24 hours or on day-1 postsurgery

Secondary endpoints

1) change in CKMB in ng/ml at 24-hours or on day-1 postsurgery
2) change in IL-6 in pg/ml at 24-hours or on day-1 postsurgery
3) change in TNFα in pg/ml at 24-hours or on day-1 postsurgery
4) length of stay in ICU (days/hours)
5) length of hospitalization (days)
6) mortality

Subgroup analyses

1) a sub-analysis of the primary and secondary data points in a coronary artery bypass graft surgery (on- and off-pump) subgroup.

9.4 Results

9.4.1 Analysis of included studies

Fifteen studies were included with 1464 patients. The baseline characteristics of the study patients are shown in Table 9.2. The mean age for the patients varied between 50 and 70 years. The percentage of males reported in the studies ranged from 47 to 71. Less than half of the studies (7/15) reported on patients' preoperative LVEF values. Five studies (178, 289-292) reported use of calcium channel blockers, angiotensin converting enzyme inhibitor/angiotensin receptor blocker, β blockers, statins, nitrates or anti-platelet drugs. In four of these there was no statistical difference in use of these drugs between groups (289-292), whereas Kim *et al.* (178) found a significant percentage of patients in the control group to be on angiotensin receptor blocker and anti-platelet drugs.

Twelve studies used a placebo as a comparator (106, 166, 171, 178, 180, 287, 289, 291-295). Only three of the studies included (106, 294, 296) compared dexmedetomidine with placebo in the absence of other cardioprotective agents such as volatile agents (148) and morphine (49), while one study was unclear on its methodology (292). Only one study reported on long-

term mortality (178). A judgement of “low” risk of bias was made on eight of the studies (Table 9.1). OPCAB was performed in four studies (166, 178, 287, 294). CABG surgery (on-pump) was performed in two studies (180, 297).

Table 9.1: Methodological quality assessment of trials by author

(+) = low risk of bias, (?) = unclear, (-) = high risk of bias. Total number of patients = 1464

Author and year of publication	Number of patients	Random sequence allocation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Concealment method
Tosun 2012	38	+	+	+	+	+	+	+	Unclear
Khalil 2013	50	+	+	+	+	+	+	+	Unclear
Ren 2013	162	+	?	?	?	+	+	+	Unclear
Kim 2014	153	+	+	+	+	+	+	+	Computer generated
Ueki 2014	37	+	+	+	+	+	+	+	Sealed envelope
Cho 2016	200	+	?	?	?	+	+	+	Unclear
Bulow 2016	23	+	?	?	?	+	+	+	Unclear
Chi 2016	100	+	?	?	?	+	+	+	Computer generated
Ammar 2016	50	+	+	+	+	+	+	+	Computer generated
Soliman 2017	150	+	+	+	+	+	+	+	Coin tossing
Li 2017	285	+	+	+	+	+	+	+	Sealed letters
Wang 2017	96	+	-	-	-	-	+	+	None
Huang 2017	30	+	+	+	?	+	+	+	Sealed envelope
Turktan 2017	60	+	-	-	-	-	+	+	None
Zhang 2013	30	+	?	?	?	?	?	?	Unclear

Table 9.2: Characteristics of enrolled studies

1st author, year (ref)	Age	Male (%)	LVEF (%)	CPB (min)	Surgical type	Sample
Tosun. 2013 (180)	62(10)	71	55(9)	128(35)	CABG	38
Khalil 2013 (294)	59(10)	62	56(6)	n/a	OPCAB	50
Ren 2013 (166)	59(5)	33	-	n/a	OPCAB	162
Kim 2014 (178)	65(4)	80	-	n/a	OPCAB	153
Ueki 2014 (171)	70(11)	43	-	134(80)	Valve + CABG	37
Cho 2016 (292)	61(13)	48	62(11)	131(53)	Valve ±CABG, aorta	200
Bulow 2016 (106)	62(7)	65	-	91(23)	CABG mini-CPB	23
Chi 2016 (287)	55(7)	60	57(8)	n/a	OPCAB	100
Ammar 2016 (289)	57(7)	76	-	66(6)	CPB cases	50
Soliman 2017 (290)	53(10)	51	45(4)	-	Valve + CABG	150
Li 2017 (291)	64(4)	69	67(5)	104(14)	Valve + CABG	285
Wang 2017 (296)	56(7)	53	-	-	Valve	96
Huang 2017 (293)	50(10)	47	59(8)	118(28)	Valve	30
Turktan 2017 (297)	57(15)	63	-	117(35)	CABG	60
Zhang 2013 (295)	45-64	-	-	-	Valve	30
					Total	1464

* LVEF – left ventricular ejection fraction; CPB – cardio-pulmonary bypass; OPCAB – off-pump coronary artery bypass graft surgery; CABG – on-pump coronary artery bypass graft surgery

9.4.2 Meta-analysis of the impact of intraoperative dexmedetomidine on outcomes

Data synthesis and meta-analyses were performed (Figures 9.2 to 9.16). There was a statistically significant reduction in changes in cTn, TNFα and IL-6 levels at 24-hours/day-1 postsurgery in the dexmedetomidine group compared to control (MD -0.35; 95% CI -0.44, -0.25; $p<0.00001$, $I^2 = 94\%$), (SMD -2.37; 95% CI -3.60, -1.15; $p<0.001$, $I^2=76\%$) and (SMD -1.26; 95% CI -1.97, -0.55; $p=0.0005$, $I^2=42\%$) respectively. There was, however, significant heterogeneity in troponin and TNFα estimates. Intraoperative dexmedetomidine showed a statistically significant decrease in length of ICU stay (hours) compared to control (SMD -0.98; 95% CI -1.84, -0.12; $p=0.03$, $I^2 = 94\%$) with significant heterogeneity.

There was a tendency towards a reduction in short-term mortality and length of hospitalisation in the dexmedetomidine group (OR 0.36; 95% CI 0.11, 1.13; p=0.08; I^2=0%) and (SMD -0.30; 95% CI -0.64, -0.03; p=0.07, I^2 = 79%) respectively. No significant differences were found in the estimates for 24-hour CKMB and IL6 change, LOS in ICU (days), and long term mortality.

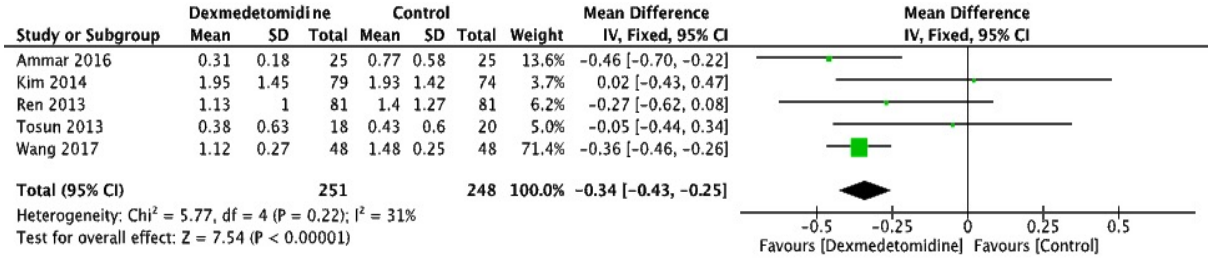


Figure 9.2: Analysis of cTn change 24 hours (ng/ml)

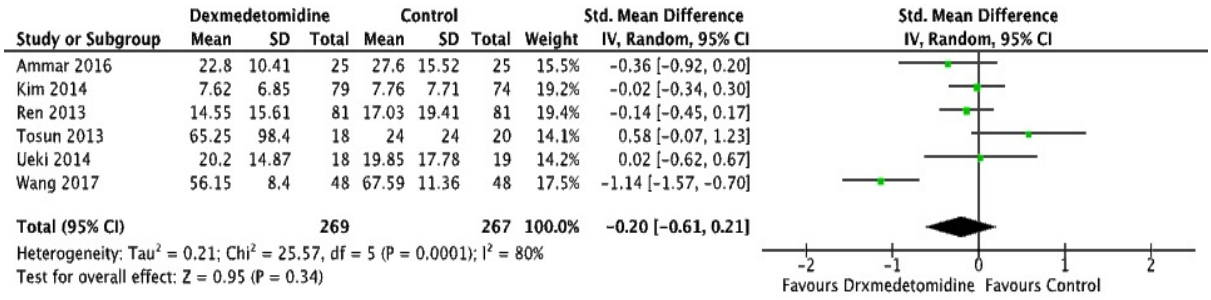


Figure 9.3: Analysis of CKMB change 24 hours (ng/ml)

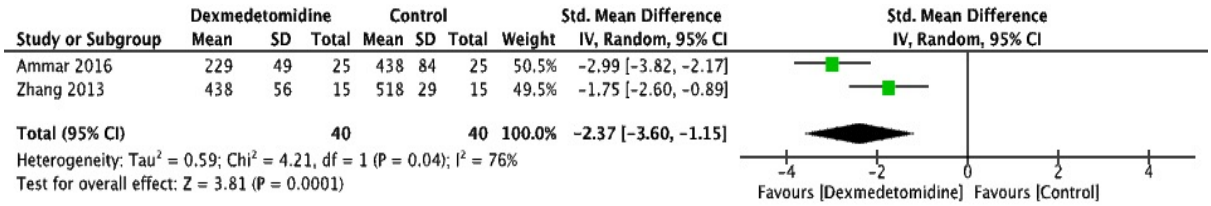


Figure 9.4: Analysis of TNFα change 24 hours (pg/ml)

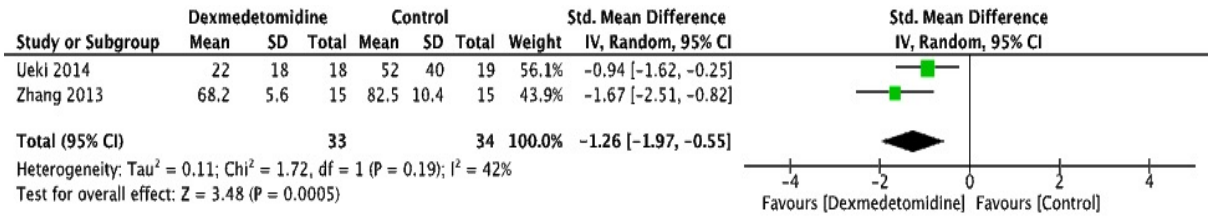


Figure 9.5: Analysis of IL-6 change 24 hours (pg/ml)

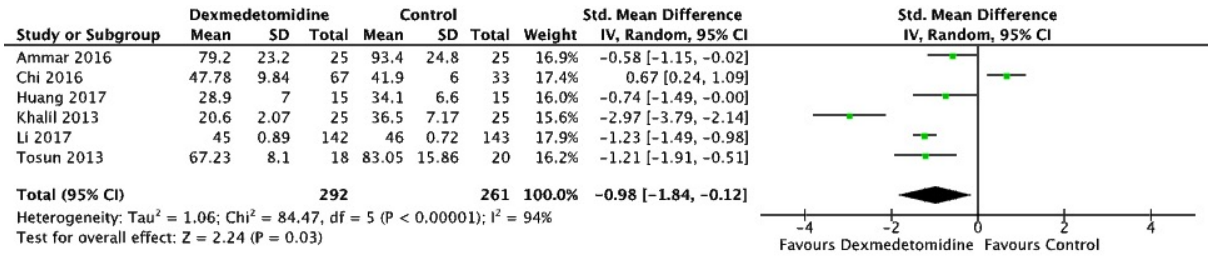


Figure 9.6: Analysis of length of stay in ICU (hours)

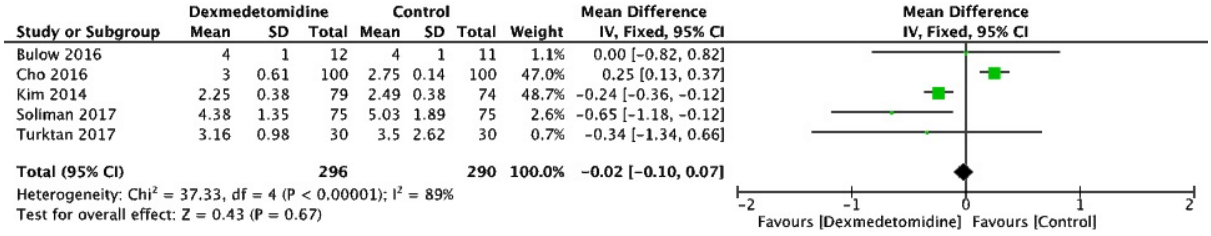


Figure 9.7: Analysis of length of stay in ICU (days)

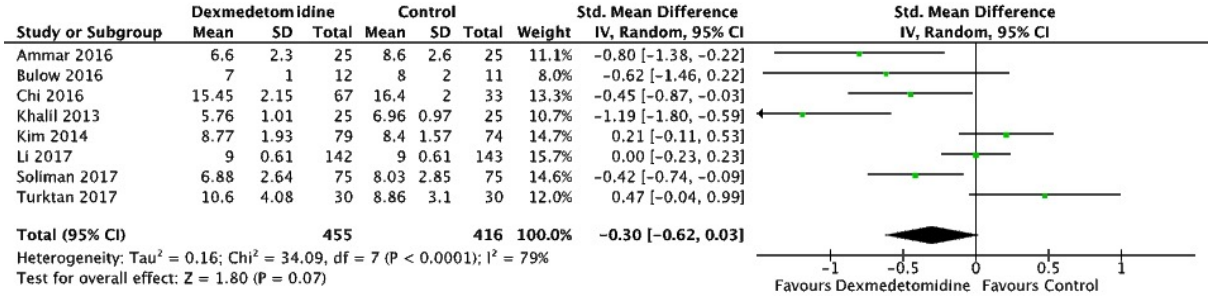


Figure 9.8: Analysis of length of stay in hospital (days)

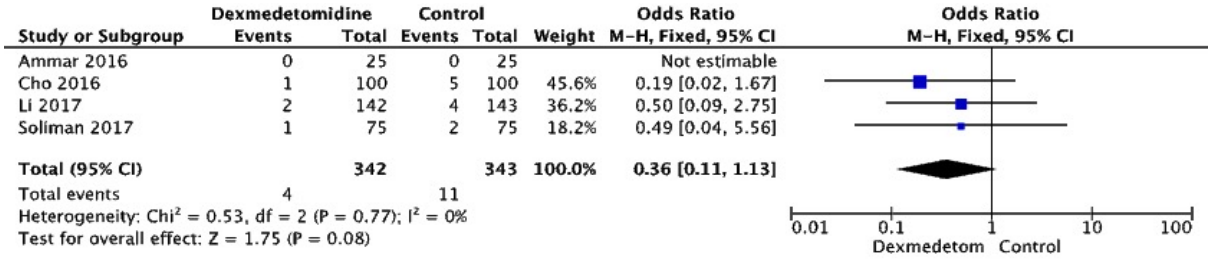


Figure 9.9: Analysis of short-term mortality

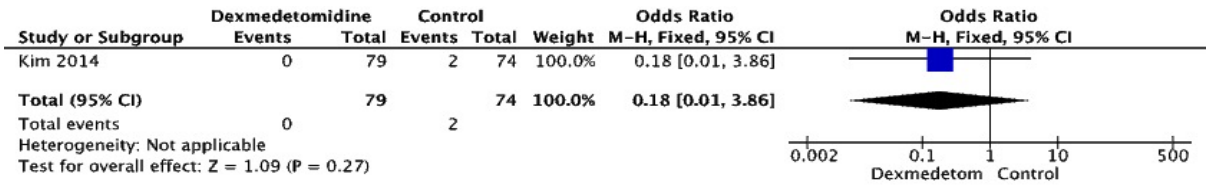


Figure 9.10: Analysis of long-term mortality

Eight (8) studies were included in the analysis for length of hospitalisation and a funnel plot of studies reporting on hospitalisation showed no publication bias (Figure 9.11).

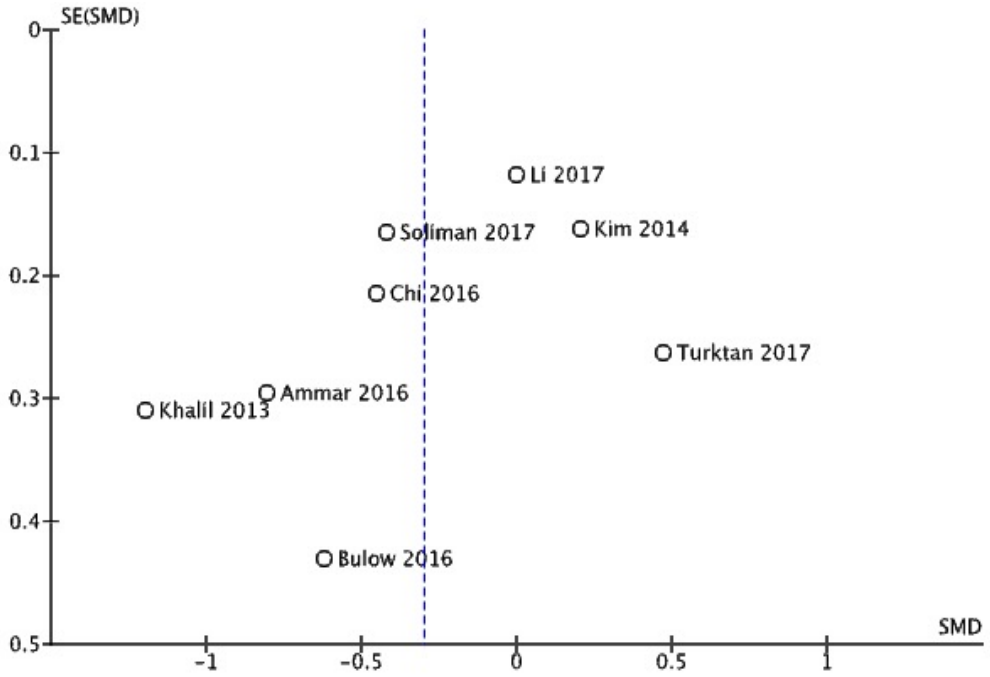


Figure 9.11: Funnel plot: length of hospital stay (days)

9.4.3 Coronary artery bypass graft subgroup analyses

Dexmedetomidine statistically significantly reduced length of stay in ICU (days) (MD -0.24; 95% CI -0.35, -0.12; p<0.0001). Although the results show a tendency towards a reduction in length of hospitalisation and changes in ischaemic biomarkers cTn and CKMD at 24-hours/day-1 in the dexmedetomidine group, they did not reach statistical significance.

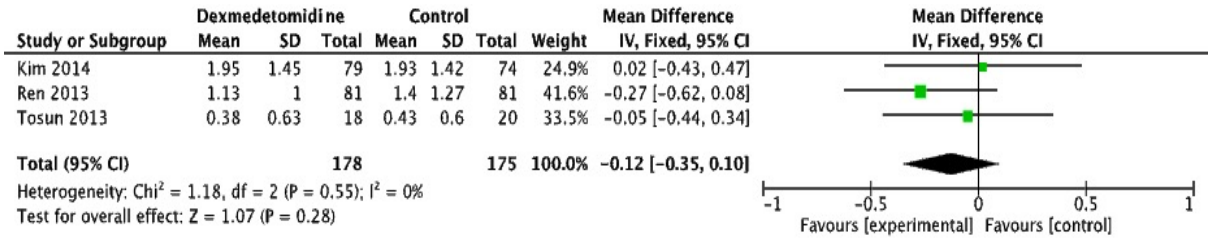


Figure 9.12: Analysis of cTn change 24 hours coronary subgroup (ng/ml)

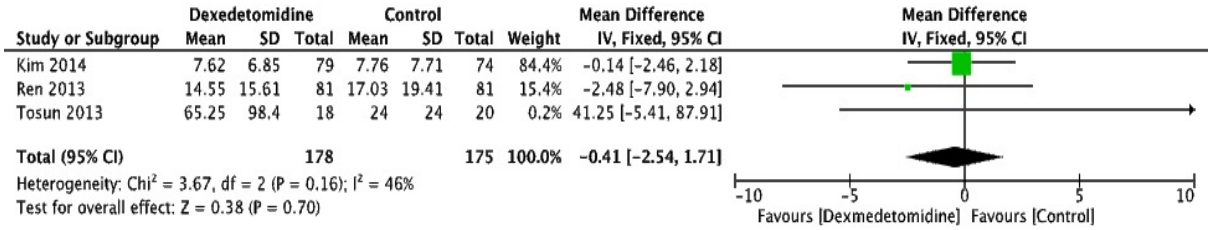


Figure 9.13: Analysis of CKMB change 24 hours coronary subgroup (ng/ml)

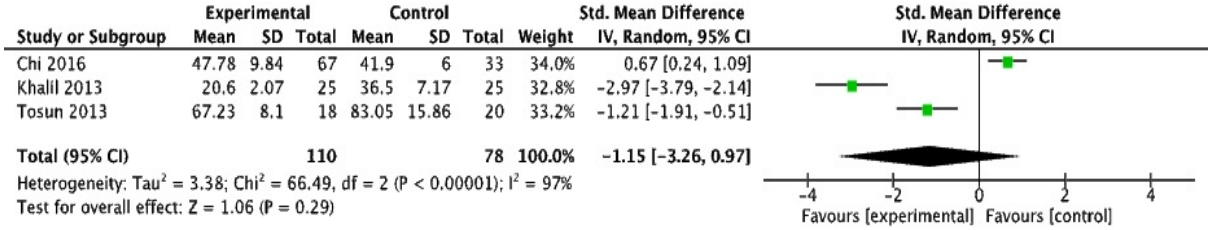


Figure 9.14: Analysis of length of stay in ICU coronary subgroup (hours)

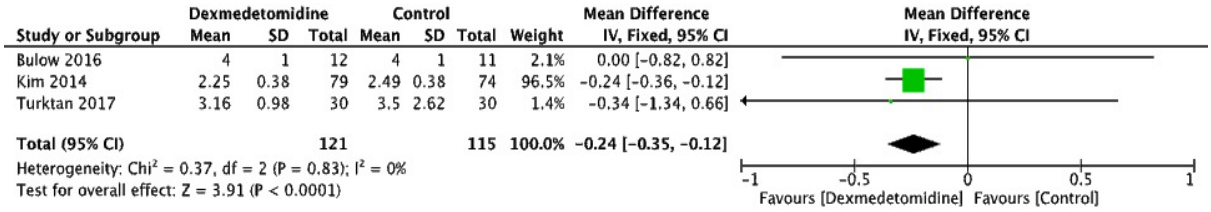


Figure 9.15: Analysis of length of stay in ICU coronary subgroup (days)

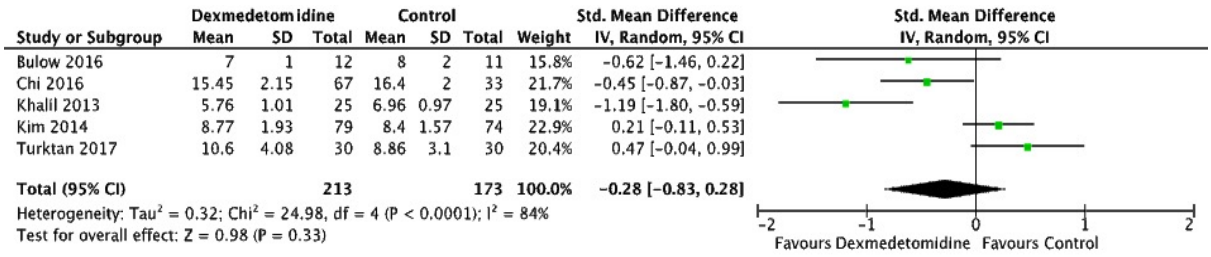


Figure 9.16: Analysis of length of stay in hospital coronary subgroup (days)

9.5 Reliability of data

The event rate for the analysis of short-term **mortality** in the dexmedetomidine group was 1% and 3% in the control group with the difference in event rate of (2%). To obtain a power of 80% and a two-sided α of 0.05 with this difference, we would need an estimated sample size of 1436 patients with 719 in the placebo group and 717 in the dexmedetomidine group.

9.6 Discussion

Our meta-analysis included RCTs where dexmedetomidine was administered intraoperatively during cardiac surgery. A total sample size of 1434 patients was included in the 14 studies. This meta-analysis is the first to provide an analysis of RCTs on the impact of intraoperative dexmedetomidine on outcomes in cardiac surgery. The meta-analysis was underpowered. Previous published systematic reviews and meta-analyses have included intraoperative cardiac studies together with postoperative ICU sedation studies (239, 298, 300, 301), with a resultant clinical and statistical heterogeneity.

Our analysis included all types of adult cardiac surgery on and off CPB in adult patients. The analysis was not a dose finding study, nor did it discriminate against timing and duration of intraoperative administration. The different types of cardiac surgery, different populations, control/comparator drugs, outcome measures and timing and dosage of the intervention drug placed our meta-analysis in the same predicament of heterogeneity.

An example of this is the variability of myocardial injury during cardiac surgery, which is known to be particularly lower during OPCAB surgery than in other cardiac surgical procedures (298). Different infusion rates of dexmedetomidine were used in different studies and ranged from 0.2μg/kg/hr to 0.9μg/kg/hr. Initiation of infusion was preinduction in some (170, 290, 291, 295, 297), postinduction in others (178, 289), and extended to 24-hours in ICU in one study (292). Myocardial protection outcomes were not the primary outcome in a number of included trials as one was set out to look at renal outcomes (292), whereas another looked at delirium as an outcome (291).

A number of studies investigated the effects of dexmedetomidine on biomarkers in cardiac surgery. However, several of them reported their results in the form of graphs with no backup raw data to allow for inclusion in the analysis (170-172, 177, 287, 293). The lack of response from authors who reported on cardiac and inflammatory biomarkers in the form of graphs may have created a bias as the addition of these outcomes in this meta-analysis may have had a different result. In particular, our analysis reports on changes in TNF-α with the exclusion of a study by Farsad *et al.* (172), who had found an increase in TNF-α in their

dexmedetomidine group in comparison with placebo, whereas the studies we included had found a decrease.

The effect of non-surgical strategies (drugs) employed intraoperatively in the studies included was not quantified to assess if these did not confound the impact of dexmedetomidine on outcomes. A recent consensus process has found the following parameters to reduce mortality in cardiac surgery: "aspirin, glycaemic control, high-volume surgeons, prophylactic intra-aortic balloon pump, levosimendan, leuko-depleted red blood cells transfusion, non-invasive ventilation, tranexamic acid, vacuum-assisted closure, and volatile agents"(148).

In nine studies anaesthesia was maintained with a volatile agent (106, 171, 177, 178, 180, 287, 290, 291, 293, 295). Volatile agents are known to confer myocardial protection through preconditioning (146, 148). Morphine, with its effects on attenuation of ischaemic and inflammatory effects, was also used in combination with sevoflurane in a study by Chi *et al*. (177, 287). Methylprednisone was added intraoperatively in two studies (180, 297).

A subgroup analysis of coronary artery bypass graft surgery cases was performed. We found a statistically significant association with a reduction in length of stay in ICU. This result, with a homogenous dataset, has not been reported before in a meta-analysis but follows on the results of a meta-analysis that recruited predominantly cardiac surgical sedation studies (239).

Interpretation of these results should take into consideration drugs used for sedation in ICU, which often include opioids and benzodiazepines leading to prolonged sedation (298, 302). It is also important to note the tendency towards a protective effect of dexmedetomidine evidenced by analysis of ischaemic biomarkers, which may on the other hand contribute towards reduced LOS in ICU.

Although the meta-analysis of the included RCTs goes a long way in signalling the impact of dexmedetomidine in cardiac surgery, the results should be interpreted with caution. The

heterogeneity related to methodology, participants, control drugs and outcomes of the trials included precludes generalisation of the results and therefore mandates a study with a large sample size (303).

9.7 Conclusion

Intraoperative administration of dexmedetomidine in adult cardiac surgery patients significantly reduced length of stay in ICU (hours) and attenuated increases in troponin, TNFα and IL-6 levels on postoperative day 1 in this meta-analysis.

Although there is a signal of improved outcome in cardiac patients who received dexmedetomidine intraoperatively, the sample sizes are small, and the heterogeneity is marked in most of the analyses for one to draw generalised conclusions. Further research with large sample sizes is likely to have an important impact on our confidence in the estimate of effects found in this meta-analysis.

We therefore await the reporting of results of the "Dexmedetomidine and Outcomes of Cardiac Surgery (DOCS)" trial (ClinicalTrials.gov Identifier: NCT02237495) which is expected to enrol 1000 patients and be complete in 2018 as well as the "Low Dose Dexmedetomidine and Delirium After Cardiac Surgery (LOWDEXDEL)" trial (ClinicalTrials.gov Identifier: NCT03388541) which is expected to be complete in 2019.

CHAPTER 10 : SUMMARY OF RESULTS

10.1 Findings in this current study

10.1.1 Addressing the gap in knowledge

- In this current study, we described the effects of dexmedetomidine on hs-cTnT that have not been described before, and calculated a post-hoc sample size for a power of 80% with an α angle of 0.05 given the difference in means that we found.

- In a sub-analysis of the our dexmedetomidine group from the clinical trial, we investigated the additional influence ethnicity potentially had on changes in troponin, which has not been found in the literature.

- In a sub-analysis of the CABG surgery group we described the impact of dexmedetomidine on cTn for the pooled data, which has not been described before.

- In a systematic review and meta-analysis, we determined the estimates for the effect of dexmedetomidine on mortality in cardiac surgery, which has not been described before, although the analysis was under-powered.

10.1.2 The impact of dexmedetomidine on outcomes in CABG surgery

- We did not find evidence that dexmedetomidine attenuated the rise in ischemic biomarker levels.

- There was no evidence that dexmedetomidine modulated the inflammatory response to surgery as evidenced by the lack of difference in IL-6 and IL-10.

- Length of ICU stay was longer in patients who received dexmedetomidine. Although this result did not reach statistical significance, it suggests that dexmedetomidine might be detrimental.

- There was no difference in the rate of adverse events between dexmedetomidine vs. placebo group, implying that dexmedetomidine was not protective.

- Patients who received dexmedetomidine were hospitalized for a longer period. Their baseline characteristics, including renal function, were not statistically different – once again implying that dexmedetomidine could be detrimental. However, the effects of other sedative drugs used in ICU and their confounding properties were not explored.

- Aortic cross-clamp time and cardiopulmonary bypass time had a strong relationship with length of stay in ICU and adverse outcome.

- There was also a significant relationship between baseline hs-cTnT, a marker of myocardial injury, with CRP, a known inflammatory marker in endothelial disease and atherogenesis, and NT-proBNP, an indicator of myocardial wall tension that acts to modulate a multisystem response to cardiac failure. This might indicate that the preoperative status of the patients subsequently determines their perioperative course and outcomes.

- This current study has shown an association between dexmedetomidine administration and prolonged hospital stay in the first week. The study was not designed to compare dexmedetomidine with drugs used in ICU, but with placebo. Previous literature has, however, shown dexmedetomidine to prolong length of stay when compared with propofol and remifentanil. Propofol and remifentanil were used in our ICU but their effects were not analysed. These drugs may have contributed to the prolonged length of stay found in our study. The possible effects of the prolonged context-sensitive half-life of dexmedetomidine post infusion did not form part of our study.

- There was a significant association between biomarkers and outcome, consistent with the literature: preoperative hs-cTnT and NT-proBNP levels, as well as delta hs-cTnT levels, were independent predictors of 30-day mortality. Ejection fraction and age were found to be significant independent predictors of 30-day mortality.

10.1.3 Pharmacoethnicity

- The baseline hs-cTnT in African patients was statistically significantly higher than in the other ethnic groups of Whites and Indians. The change in troponin over 24 hours postoperatively between these two groups was not statistically significant.

- African patients in the dexmedetomidine group also had a statistically significantly higher NT-proBNP when compared to those in the non-dexmedetomidine group. This did not translate into worse clinical outcomes.

- Although this current study was not powered to show statistical difference in this regard, as this was a sub-analysis, the results are meant to be hypothesis forming in this relatively new field of study.

- There was no difference on the impact of dexmedetomidine administration either on bio-marker levels or clinical outcomes when patients where compared according to gender.

10.1.4 Ethnic and gender differences in cardiovascular risk factor profile

- African patients were marginally older at presentation than the combined group of white and Indian patients.

- There was a significantly higher prevalence of diabetes mellitus in Indian patients (68%) compared with the other 2 ethnic groups.

- Female patients presented with a significantly higher prevalence of dyslipidaemia than males. However, there were no significant differences between gender groups with regard to BMI.

- African patients also presented with marginally raised perioperative biomarker profiles (CRP and hs-cTnT), when compared with other ethnic groups.

10.1.5 Meta-analysis of the effects of dexmedetomidine on outcomes in cardiac surgery with a coronary artery bypass graft surgery sub-analysis

- There was a tendency towards better mortality outcomes in patients that received dexmedetomidine.

- Although there is this signal of improved mortality and other outcomes in cardiac patients that received dexmedetomidine intraoperatively, the analysis is underpowered, and the heterogeneity is marked in most of the analyses for one to draw generalised conclusions.

- Further research with large sample sizes is likely to have an important impact on our confidence in the estimate of effects found in this meta-analysis.

- The common limitation between this clinical trial, previous prospective clinical studies and this meta-analysis is that of inadequate power. More studies are necessary for the purposes of pooling data and larger studies with less clinical and statistical bias are still warranted.

10.2 Conclusions

Dexmedetomidine did not show a reduction in the postoperative hs-cTnT profile or better clinical outcomes when compared with placebo. In a meta-analysis, a subgroup analysis of the

impact of dexmedetomidine on cTn and CKMD at 24-hours/day-1 in CABG did not show statistically significant differences compared to other therapy.

A statistically significantly prolonged length of hospitalisation was found in the dexmedetomidine group, instead. The possible contribution of its prolonged context-sensitive half-life has to be borne in mind, together with confounding sedatives administered in ICU. Dexmedetomidine did not manifest any other clear adverse outcome, particularly with regards to mortality rates.

In a meta-analysis of randomised controlled trials, there was a tendency towards a reduction in mortality in the dexmedetomidine group with no heterogeneity. Intraoperative administration of dexmedetomidine in adult cardiac surgery patients showed a statistically significantly reduced length of stay in ICU(hours) and attenuated increases in troponin, TNFα and IL-6 levels on postoperative day 1.

Generally, the small sample sizes of the studies reported create a difficulty in generalising for entire populations. Reporting of results of the "Dexmedetomidine and Outcomes of Cardiac Surgery (DOCS)" trial (ClinicalTrials.gov Identifier: NCT02237495) which is expected to enrol 1000 patients and be complete in 2018 and the "Low Dose Dexmedetomidine and Delirium After Cardiac Surgery (LOWDEXDEL)" trial (ClinicalTrials.gov Identifier: NCT03388541) which is expected to be complete in 2019, will likely give a better indication towards outcomes. Inclusion of these in the meta-analysis will strengthen the level of evidence.

10.3 Recommendations

As we await results from the DOCs and LOWDEXDEL studies, perhaps we should start investing towards exploring the concept of "multimodal cardioprotection", together with the "multi-biomarker" concept. Meanwhile, to clarify data that seem to infer one agent as superior to another, a five-winged study comparing dexmedetomidine, a volatile agent (sevoflurane), lignocaine, morphine and ketamine would be ideal. It should be planned to

investigate the impact of these agents on ischaemic markers; inflammatory markers; LOS in ICU and hospital; and mortality is warranted.

A conclusion would assist in the choice of better and more cost-effective drug combinations, particularly in low income countries. Inclusion of ongoing studies and results from studies published with unclear data into a meta-analysis of ischaemic and inflammatory marker response to dexmedetomidine infusion during CABG would also be ideal in consolidating the data and assessing the outcome of pooled data.

BIBLIOGRAPHY

1. Rantanen A, Tarkka M-T, Kaunonen M, Tarkka M, Sintonen H, Koivisto A-M, et al. Health-related quality of life after coronary artery bypass grafting. *Journal of Advanced Nursing.* 2009;65(9):1926-36.

2. Ferguson TB, Jr. Mortality in coronary artery bypass grafting: what's next? *Circulation.* 2012;125(20):2409-11.

3. Kato R, Foex P. Myocardial protection by anesthetic agents against ischemia-reperfusion injury: an update for anesthesiologists. *Canadian Journal of Anaesthesia.* 2002;49(8):777-91.

4. Bainbridge D, Martin J, Cheng D. Off pump coronary artery bypass graft surgery versus conventional coronary artery bypass graft surgery: a systematic review of the literature. *Seminars in Cardiothoracic and Vascular Anesthesia.* 2005;9(1):105-11.

5. Baufreton C, Corbeau JJ, Pinaud F. [Inflammatory response and haematological disorders in cardiac surgery: toward a more physiological cardiopulmonary bypass]. *Annales Francaises d'anesthesie et de reanimation.* 2006;25(5):510-20.

6. Corral-Velez V, Lopez-Delgado JC, Betancur-Zambrano NL, Lopez-Sune N, Rojas-Lora M, Torrado H, et al. The inflammatory response in cardiac surgery: an overview of the pathophysiology and clinical implications. *Inflammation & Allergy Drug Targets.* 2015;13(6):367-70.

7. Dabbous A, Kassas C, Baraka A. The inflammatory response after cardiac surgery. *Middle East Journal of Anaesthesiology.* 2003;17(2):233-54.

8. Bulow NMH, Colpo E, Duarte MF, Correa EFM, Schlosser RS, Lauda A, et al. Inflammatory Response in Patients under Coronary Artery Bypass Grafting Surgery and Clinical Implications: A Review of the Relevance of Dexmedetomidine Use. *ISRN Anesthesiology.* 2014;2014:1-28.

9. Aantaa R, Jalonen J. Perioperative use of alpha(2)-adrenoceptor agonists and the cardiac patient. *European Journal of Anaesthesia.* 2006;23(5):361-72.

10. Biccard BM, Goga S, de Beurs J. Dexmedetomidine and cardiac protection for non-cardiac surgery: a meta-analysis of randomised controlled trials. *Anaesthesia.* 2008;63(1):4-14.

11. Chen S, Hua F, Lu J, Jiang Y, Tang Y, Tao L, et al. Effect of dexmedetomidine on myocardial ischemia-reperfusion injury. *International Journal of Clinical and Experimental Medicine.* 2015;8(11):21166-72.

12. Ji F, Li Z, Nguyen H, Young N, Shi P, Fleming N, et al. Perioperative Dexmedetomidine Improves Outcomes of Cardiac Surgery. *Circulation.* 2013;127(15):1576-84.

13. Kabukcu HK, Sahin N, Temel Y, Titiz TA. Hemodynamics in coronary artery bypass surgery: effects of intraoperative dexmedetomidine administration. *Der Anaesthesist.* 2011;60(5):427-31.

14. Ji F, Li Z, Young N, Moore P, Liu H. Perioperative dexmedetomidine improves mortality in patients undergoing coronary artery bypass surgery. *Journal of Cardiothoracic and Vascular Anesthesia.* 2014;28(2):267-73.

15. Priebe HJ. Perioperative myocardial ischemia and infarction. *Anesthesia and Analgesia.* 2005:62-70.

16. Causes of death – WHO [Internet]. [cited 2016Oct17]. Available from: http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_part2.

17. Health Profile South Africa [Internet]. World life expectancy. [cited 2016Jan20]. Available from: http://www.worldlifeexpectancy.com/country-health-profile/south-africa.

18. Hughes BB, Kuhn R, Peterson CM, Rothman DS, Solorzano JR, Mathers CD, et al. Projections of global health outcomes from 2005 to 2060 using the International Futures integrated forecasting model. *Bulletin of the World Health Organization.* 2011;89(7):478-86.

19. The burden of coronary artery disease: a global killer – an international epidemic – high cost burden | CLARIFY registry official web site [Intenet]. CLARIFY registry official

web site RSS. [cited 2016Nov19]. Available from: http://www.clarify-registry.com/healthcare-professionals/about-coronary-artery-disease/1-the-burden-of-cad/#.

20. Lopez AD, Mathers CD. Measuring the global burden of disease and epidemiological transitions: 2002-2030. *Annals of Tropical Medicine Parasite.* 2006;100(5-6):481-99.

21. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *Public Library of Science Medicine.* 2006;3(11).

22. Chesler E, Mitha AS, Weir EK, Matisonn RE, Hitchcock PJ. Myocardial-Infarction in Black-Population of South-Africa - Coronary Arteriographic Findings. *American Heart Journal.* 1978;95(6):691-6.

23. Joubert J, McLean CA, Reid CM, Davel D, Pilloy W, Delport R, et al. Ischemic heart disease in black South African stroke patients. *Stroke.* 2000;31(6):1294-8.

24. Akinboboye O, Idris O, Akinboboye O, Akinkugbe O. Trends in coronary artery disease and associated risk factors in sub-Saharan Africans. *Journal of Human Hypertension.* 2003;17(6):381-7.

25. Steyn K, Sliwa K, Hawken S, Commerford P, Onen C, Damasceno A, et al. Risk factors associated with myocardial infarction in Africa: the INTERHEART Africa study. *Circulation.* 2005;112(23):3554-61.

26. Nethononda MR, Essop MR, Mbewu AD, Galpin JS. Coronary artery disease and risk factors in Black South Africans - A comparative study. *Ethnic Disease.* 2004;14(4):515-9.

27. Vorster HH. The emergence of cardiovascular disease during urbanisation of Africans. *Public Health Nutrition.* 2002;5(1A):239-43.

28. Sliwa K, Wilkinson D, Hansen C, Ntyintyane L, Tibazarwa K, Becker A, et al. Spectrum of heart disease and risk factors in a black urban population in South Africa (the Heart of Soweto Study): a cohort study. *Lancet.* 2008;371(9616):915-22.

29. Alberts M, Urdal P, Steyn K, Stensvold I, Tverdal A, Nel JH, et al. Prevalence of cardiovascular diseases and associated risk factors in a rural black population of South Africa.

European Journal of Cardiovascular Prevention and Rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology. 2005;12(4):347-54.

30. Gillies M, Bellomo R, Doolan L, Buxton B. Bench-to-bedside review: Inotropic drug therapy after adult cardiac surgery -- a systematic literature review. *Critical Care (London, England).* 2005;9(3):266-79.

31. Priebe HJ. Perioperative myocardial infarction - aetiology and prevention. *British Journal of Anaesthesia.* 2005;95(1):3-19.

32. Ferguson TB. Mortality in Coronary Artery Bypass Grafting What's Next? *Circulation.* 2012;125(20):2409-11.

33. Cheng DC, Bainbridge D, Martin JE, Novick RJ, Evidence-Based Perioperative Clinical Outcomes Research G. Does off-pump coronary artery bypass reduce mortality, morbidity, and resource utilization when compared with conventional coronary artery bypass? A meta-analysis of randomized trials. *Anesthesiology.* 2005;102(1):188-203.

34. Donndorf P, Kuhn F, Vollmar B, Rosner J, Liebold A, Gierer P, et al. Comparing microvascular alterations during minimal extracorporeal circulation and conventional cardiopulmonary bypass in coronary artery bypass graft surgery: a prospective, randomized study. *The Journal of Thoracic and Cardiovascular Surgery.* 2012;144(3):677-83.

35. Motshabi P. Myocardial ischaemia during coronary artery bypass graft surgery: a review of pathophysiology (Part 1). *South African Journal of Anaesthesia and Analgesia.* 2012;18(2):70-74.

36. Laffey JG, Boylan JF, Cheng DC. The systemic inflammatory response to cardiac surgery: implications for the anesthesiologist. *Anesthesiology.* 2002;97(1):215-52.

37. Maharaj C, Laffey JG. New strategies to control the inflammatory response in cardiac surgery. *Current Opinion in Anaesthesiology.* 2004;17(1):35-48.

38. Desborough JP. The stress response to trauma and surgery. *British Journal of Anaesthesia.* 2000;85(1):109-17.

39. Priebe HJ. Incidence and ranking of perioperative myocardial ischaemias. *Anasthesia and Intensive Care Journal.* 1999;34(3):177-81.

40. Priebe HJ. Triggers of perioperative myocardial ischaemia and infarction. *British Journal of Anaesthesia.* 2004;93(1):9-20.

41. Kloner RA, Jennings RB. Consequences of brief ischemia: stunning, preconditioning, and their clinical implications: part 1. *Circulation.* 2001;104(24):2981-9.

42. Kloner RA, Jennings RB. Consequences of brief ischemia: stunning, preconditioning, and their clinical implications: part 2. *Circulation.* 2001;104(25):3158-67.

43. Kloner RA, Bolli R, Marban E, Reinlib L, Braunwald E. Medical and cellular implications of stunning, hibernation, and preconditioning: an NHLBI workshop. *Circulation.* 1998;97(18):1848-67.

44. Rosenkranz ER, Buckberg GD. Myocardial protection during surgical coronary reperfusion. *Journal of the American College of Cardiology.* 1983;1(5):1235-46.

45. Abramov D, Abu-Tailakh M, Frieger M, Ganiel A, Tuvbin D, Wolak A. Plasma troponin levels after cardiac surgery vs after myocardial infarction. *Asian Cardiovascular & Thoracic Annals.* 2006;14(6):530-5.

46. Lasocki S, Provenchere S, Benessiano J, Vicaut E, Lecharny JB, Desmonts JM, et al. Cardiac troponin I is an independent predictor of in-hospital death after adult cardiac surgery. *Anesthesiology.* 2002;97(2):405-11.

47. Croal BL, Hillis GS, Gibson PH, Fazal MT, El-Shafei H, Gibson G, et al. Relationship between postoperative cardiac troponin I levels and outcome of cardiac surgery. *Circulation.* 2006;114(14):1468-75.

48. Fellahi JL, Leger P, Philippe E, Arthaud M, Riou B, Gandjbakhch I, et al. Pericardial cardiac troponin I release after coronary artery bypass grafting. *Anesthesia and Analgesia.* 1999;89(4):829-34.

49. Motshabi P. Myocardial ischaemia during coronary artery bypass graft surgery: a review of intervention strategies (Part 2). *Southern African Journal of Anaesthesia and Analgesia*. 2012;18(3):134-138.

50. Naghshtabrizi B, Sohrabi Z, Emami F, Manafi B, Membari S. Evaluation of the incidence of major adverse cardiac and cerebrovascular events after percutaneous coronary intervention or coronary artery bypass graft on proximal left anterior descending artery with and without other coronary arteries involvement. *International Cardivascular Research Journal.* 2016;10(2):61-6.

51. Bortnick AE, Epps KC, Selzer F, Anwaruddin S, Marroquin OC, Srinivas V, et al. Five-Year Follow-Up of Patients Treated for Coronary Artery Disease in the Face of an Increasing Burden of Co-Morbidity and Disease Complexity (from the NHLBI Dynamic Registry). *American Journal of Cardiology.* 2014;113(4):573-9.

52. Kirno K, Friberg P, Grzegorczyk A, Milocco I, Ricksten SE, Lundin S. Thoracic epidural anesthesia during coronary artery bypass surgery: effects on cardiac sympathetic activity, myocardial blood flow and metabolism, and central hemodynamics. *Anesthesia and Analgesia.* 1994;79(6):1075-81.

53. Mohammed AA, Agnihotri AK, van Kimmenade RRJ, Martinez-Rumayor A, Green SM, Quiroz R, et al. Prospective, comprehensive assessment of cardiac troponin T testing after coronary artery bypass graft surgery. *Circulation.* 2009;120(10):843-50.

54. Suttorp MJ, Kingma JH, Vos J, Koomen EM, Tijssen JG, Vermeulen FE, et al. Determinants for early mortality in patients awaiting coronary artery bypass graft surgery: a case-control study. *European Heart Journal.* 1992;13(2):238-42.

55. Suttorp MJ, Kingma JH, Koomen EM, Tijssen JG, Defauw JA, Ernst JM. [Predictive characteristics for early mortality in patients on the waiting list for aortocoronary bypass surgery]. *Nederlands tijdschrift voor geneeskunde.* 1989;133(49):2441-5.

56. Koomen EM, Hutten BA, Kelder JC, Redekop WK, Tijssen JG, Kingma JH. Morbidity and mortality in patients waiting for coronary artery bypass surgery. *European Journal of Cardio-Thoracic Surgery : official journal of the European Association for Cardio-thoracic Surgery.* 2001;19(3):260-5.

57. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. *Global Heart*. 2012;7(4):275-95.

58. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. *Circulation.* 2012;126(16):2020-35.

59. Mookadam F, Carpenter SD, Thota VR, Cha S, Jiamsripong P, Alharthi MS, et al. Risk of adverse events after coronary artery bypass graft and subsequent noncardiac surgery. *Future Cardiology.* 2011;7(1):69-75.

60. Nicolini F, Beghi C, Muscari C, Agostinelli A, Budillon AM, Spaggiari I, et al. Myocardial protection in adult cardiac surgery: current options and future challenges. *European Journal of Cardio-Thoracic Surgery.* 2003;24(6):986-93.

61. Kunst G, Klein AA. Peri-operative anaesthetic myocardial preconditioning and protection - cellular mechanisms and clinical relevance in cardiac anaesthesia. *Anaesthesia.* 2015;70(4):467-82.

62. Hoffman D, Fernandes S, Frater RWM, Sisto D. Myocardial Protection in Diffuse Coronary-Artery Disease - Intermittent Retrograde Cold-Blood Cardioplegia at Systemic Normothermia Versus Intermittent Antegrade Cold-Blood Cardioplegia at Moderate Systemic Hypothermia. *Texas Heart Institute Journal.* 1993;20(2):83-8.

63. Naguib AN, Tobias JD, Hall MW, Cismowski MJ, Miao YJ, Barry N, et al. The Role of Different Anesthetic Techniques in Altering the Stress Response During Cardiac Surgery in Children: A Prospective, Double-Blinded, and Randomized Study. *Pediatric Critical Care Medicine.* 2013;14(5):481-90.

64. Brusset A, Abi-Jaoude F, Ceddaha A, Schlumberger S, Raffin L, Fischler M. [Clonidine aggravates the postoperative hemodynamic profile after coronary bypass: randomized, double-blind study].

La clonidine aggrave le profil hemodynamique post-operatoire apres pontage coronaire: etude randomisee en double aveugle. *Annales Francaises d'anesthesie et de reanimation.* 1989;8 Suppl:R215.

65. Zaugg M, Schulz C, Wacker J, Schaub MC. Sympatho-modulatory therapies in perioperative medicine. *British Journal of Anaesthesia.* 2004;93(1):53-62.

66. Chaney MA. Intrathecal and epidural anesthesia and analgesia for cardiac surgery. *Anesthesia and Analgesia.* 2006;102(1):45-64.

67. Scott NB, Turfrey DJ, Ray DA, Nzewi O, Sutcliffe NP, Lal AB, et al. A prospective randomized study of the potential benefits of thoracic epidural anesthesia and analgesia in patients undergoing coronary artery bypass grafting. *Anesthesia and Analgesia.* 2001;93(3):528-35.

68. Loick HM, Schmidt C, Van Aken H, Junker R, Erren M, Berendes E, et al. High Thoracic Epidural Anesthesia, but Not Clonidine, Attenuates the Perioperative Stress Response Via Sympatholysis and Reduces the Release of Troponin T in Patients Undergoing Coronary Artery Bypass Grafting. *Anesthesia & Analgesia.* 1999;88(4):701-9.

69. Al-Sabti H, Kuba PK, Chengode S, Sharma AK. Off-pump coronary artery bypass grafting through left antero-lateral thoracotomy (thora-cab) - case report and review of literature. *Oman Medical Journal.* 2008;23(4):278-81.

70. Bainbridge D, Cheng D, Martin J, Novick R, Evidence-based Peri-operative Clinical Outcomes Research G. Does off-pump or minimally invasive coronary artery bypass reduce mortality, morbidity, and resource utilization when compared with percutaneous coronary intervention? A meta-analysis of randomized trials. *The Journal of Thoracic and Cardiovascular Surgery.* 2007;133(3):623-31.

71. Bainbridge DT, Martin J, Cheng D. Is off-pump bypass grafting truly superior to conventional coronary artery bypass grafting? *The Annals of Thoracic Surgery.* 2005;79(1):383; author reply

72. Bainbridge D, Cheng DC. Early extubation and fast-track management of off-pump cardiac patients in the intensive care unit. *Seminars in Cardiothoracic and Vascular Anesthesia.* 2015;19(2):163-8.

73. Cremers B, Link A, Werner C, Gorhan H, Simundic I, Matheis G, et al. Pulsatile venoarterial perfusion using a novel synchronized cardiac assist device augments coronary artery blood flow during ventricular fibrillation. *Artificial Organs*. 2015;39(1):77-82.

74. Bignami E, Biondi-Zoccai G, Landoni G, Fochi O, Testa V, Sheiban I, et al. Volatile Anesthetics Reduce Mortality in Cardiac Surgery. *Journal of Cardiothoracic and Vascular Anesthesia.* 2009;23(5):594-9.

75. Inagaki Y. Cardiac Preconditioning by Anesthetic Agents: Roles of Volatile Anesthetics and Opioids in Cardioprotection. *Yonago Acta Medica.* 2007;50(3):45-55.

76. Jalonen J, Hynynen M, Kuitunen A, Heikkila H, Perttila J, Salmenpera M, et al. Dexmedetomidine as an anesthetic adjunct in coronary artery bypass grafting. *Anesthesiology.* 1997;86(2):331-45.

77. Khan ZP, Ferguson CN, Jones RM. alpha-2 and imidazoline receptor agonists. Their pharmacology and therapeutic role. *Anaesthesia.* 1999;54(2):146-65.

78. Hugues FC, Baillet J, Sardal J, Marche J. [Clinical pharmacology of adrenergic agonists and antagonists. I. Alpha-adrenergic agonists and antagonists]. *Coeur et Medicine Interne.* 1972;11(4):749-55.

79. Wijeysundera DN, Bender JS, Beattie WS. Alpha-2 adrenergic agonists for the prevention of cardiac complications among patients undergoing surgery. *The Cochrane Database of Systematic Reviews.* 2009(4):CD004126.

80. Aantaa R, Scheinin M. Alpha 2-adrenergic agents in anaesthesia. *Acta Anaesthesiologica Scandinavica.* 1993;37(5):433-48.

81. Aantaa R, Jalonen J. Perioperative use of alpha2-adrenoceptor agonists and the cardiac patient. *European Journal of Anaesthesiology.* 2006;23(5):361-72.

82. Arcangeli A, D'Alo C, Gaspari R. Dexmedetomidine Use in General Anaesthesia. *Current Drug Targets.* 2009;10(8):687-95.

83. Afonso J, Reis F. Dexmedetomidine: Current Role in Anesthesia and Intensive Care. *Revista Brasileira de Anestesiologia.* 2012;62(1):118-33.

84. Seftel HC, Keeley KJ, Walker AR. Characteristics of South African Bantu Who Have Suffered from Myocardial Infarction. *The American Journal of Cardiology.* 1963;12:148-56.

85. Schwartz MB SL. The pattern of heart disease in the urbanized (Johannesburg) African. *Medical Proceeds (Johannesburg)*. 1958;4, 275 – 278. [Internet]. [cited 2016Nov1]. Available from: https://wwwresearchgatenet/publication/285110409.

86. Seedat YK, Mayet FG, Latiff GH, Joubert G. Risk factors and coronary heart disease in Durban blacks--the missing links. *South African Medical Journal*. 1992;82(4):251-6.

87. Joubert J, McLean CA, Reid CM, Davel D, Pilloy W, Delport R, et al. Ischemic heart disease in black South African stroke patients. *Stroke.* 2000;31(6):1294-8.

88. Schrire V. Heart disease in Southern Africa with special reference to ischaemic heart disease. *South African Medical Journal*. 1971;45(23):634-44.

89. Steyn K, Sliwa K, Hawken S, Commerford P, Onen C, Damasceno A, et al. Risk factors associated with myocardial infarction in Africa - The INTERHEART Africa study. *Circulation.* 2005;112(23):3554-61.

90. Teo K, Chow CK, Vaz M, Rangarajan S, Yusuf S, Group PI-W, et al. The Prospective Urban Rural Epidemiology (PURE) study: examining the impact of societal influences on chronic noncommunicable diseases in low-, middle-, and high-income countries. *American Heart Journal.* 2009;158(1):1-7.e1.

91. Tibazarwa K, Ntyintyane L, Sliwa K, Gerntholtz T, Carrington M, Wilkinson D, et al. A time bomb of cardiovascular risk factors in South Africa: Results from the Heart of Soweto Study "Heart Awareness Days". *International Journal of Cardiology.* 2009;132(2):233-9.

92. Carter BL, Long TY, Cinciripini PM. A meta-analytic review of the CYP2A6 genotype and smoking behavior. *Nicotine and Tobacco Research*. 2004;6(2):221-7.

93. Ma Q, Lu AYH. Pharmacogenetics, Pharmacogenomics, and Individualized Medicine. *Pharmacological Reviews.* 2011;63(2):437-59.

94. Holliday SF, Kane-Gill SL, Empey PE, Buckley MS, Smithburger PL. Interpatient variability in dexmedetomidine response: a survey of the literature. *Scientific World Journal.* 2014;2014:805013.

95. Yasuda SU, Zhang L, Huang SM. The role of ethnicity in variability in response to drugs: Focus on clinical pharmacology studies. *Clinical Pharmacology & Therapeutics.* 2008;84(3):417-23.

96. Kohli U, Pandharipande P, Muszkat M, Sofowora GG, Friedman EA, Scheinin M, et al. CYP2A6 genetic variation and dexmedetomidine disposition. *European Journal of Clinical Pharmacology*. 2012;68(6):937-42.

97. Kurnik D, Muszkat M, Li C, Sofowora GG, Friedman EA, Scheinin M, et al. Genetic Variations in the alpha(2A)-Adrenoreceptor Are Associated With Blood Pressure Response to the Agonist Dexmedetomidine. *Circulation*: *Cardiovascular Genetics*. 2011;4(2):179-U245.

98. World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *Journal of the American Medical Association*. 2013;310(20):2191-4.

99. Jalonen J, Hynynen M, Kuitunen A, Heikkila H, Salmenpera M, Valtonen M, et al. Dexmedetomidine as an anesthetic adjunct in coronary artery bypass grafting. *Anesthesiology.* 1997;86(2):331-45.

100. Wijeysundera DN, Naik JS, Beattie WS. Alpha-2 adrenergic agonists to prevent perioperative cardiovascular complications: a meta-analysis. *The American Journal of Medicine.* 2003;114(9):742-52.

101. Larmann J, Theilmeier G. Inflammatory response to cardiac surgery: cardiopulmonary bypass versus non-cardiopulmonary bypass surgery. *Best Practice and Research Clinical Anaesthesiology*. 2004;18(3):425-38.

102. Ohata T, Mitsuno M, Yamamura M, Tanaka H, Kobayashi Y, Ryomoto M, et al. Beneficial effects of mini-cardiopulmonary bypass on hemostasis in coronary artery bypass grafting: Analysis of inflammatory response and hemodilution. *American Society for Artificial Internal Organs Journal*. 2008;54(2):207-9.

103. Paparella D, Yau TM, Young E. Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update. *European Journal of Cardio-Thoracic Surgery : official Journal of the European Association for Cardio-Thoracic Surgery.* 2002;21(2):232-44.

104. Augoustides JG. The inflammatory response to cardiac surgery with cardiopulmonary bypass: should steroid prophylaxis be routine? *Journal of Cardiothoracic and Vascular Anesthesia.* 2012;26(5):952-8.

105. Alexander JC, Jr. What initiates the systemic inflammatory response in cardiac surgery patients? *Chest.* 1997;112(5):1153-4.

106. Bulow NM, Colpo E, Pereira RP, Correa EF, Waczuk EP, Duarte MF, et al. Dexmedetomidine decreases the inflammatory response to myocardial surgery under mini-cardiopulmonary bypass. *Brazilian Journal of Medical and Biological Research = Revista Brasileira de pesquisas medicas e biologicas / Sociedade Brasileira de Biofisica [et al]*. 2016;49(4).

107. Talmor M, Hydo L, Barie PS. Relationship of systemic inflammatory response syndrome to organ dysfunction, length of stay, and mortality in critical surgical illness: effect of intensive care unit resuscitation. *Archives of Surgery.* 1999;134(1):81-7.

108. Asimakopoulos G, Taylor KM. Effects of cardiopulmonary bypass on leukocyte and endothelial adhesion molecules. *The Annals of Thoracic Surgery.* 1998;66(6):2135-44.

109. Franke A, Lante W, Fackeldey V, Becker HP, Thode C, Kuhlmann WD, et al. Proinflammatory and antiinflammatory cytokines after cardiac operation: different cellular sources at different times. *The Annals of Thoracic Surgery.* 2002;74(2):363-70; discussion 70-1.

110. Nesher N, Alghamdi AA, Singh SK, Sever JY, Christakis GT, Goldman BS, et al. Troponin after cardiac surgery: a predictor or a phenomenon? *The Annals of Thoracic Surgery.* 2008;85(4):1348-54.

111. Greenson N, Macoviak J, Krishnaswamy P, Morrisey R, James C, Clopton P, et al. Usefulness of cardiac troponin I in patients undergoing open heart surgery. *American Heart Journal.* 2001;141(3):447-55.

112. Domanski MJ, Mahaffey K, Hasselblad V, Brener SJ, Smith PK, Hillis G, et al. Association of myocardial enzyme elevation and survival following coronary artery bypass graft surgery. *Journal of the American Medical Association.* 2011;305(6):585-91.

113. Fellahi JL, Hedoire F, Le Manach Y, Monier E, Guillou L, Riou B. Determination of the threshold of cardiac troponin I associated with an adverse postoperative outcome after cardiac surgery: a comparative study between coronary artery bypass graft, valve surgery, and combined cardiac surgery. *Critical Care.* 2007;11(5):R106.

114. Fellahi JL, Gue X, Richomme X, Monier E, Guillou L, Riou B. Short- and long-term prognostic value of postoperative cardiac troponin I concentration in patients undergoing coronary artery bypass grafting. *Anesthesiology.* 2003;99(2):270-4.

115. Domanski MJ. Prognostic implications of troponin T and creatine kinase-MB elevation after coronary artery bypass grafting. *American Heart Journal*. 2012;164(5):636-7.

116. Dehoux M, Provenchere S, Benessiano J, Lasocki S, Lecharny JB, Bronchard R, et al. Utility of cardiac troponin measurement after cardiac surgery. *Clinica Chimica Acta; International Journal of Clinical Chemistry.* 2001;311(1):41-4.

117. Fellahi JL, Hanouz JL, Gue X, Monier E, Guillou L, Riou B. Kinetic analysis of cardiac troponin I release is no more accurate than a single 24-h measurement in predicting in-hospital outcome after cardiac surgery. *European Journal of Anaesthesiology.* 2008;25(6):490-7.

118. Thielmann M, Massoudy P, Neuhauser M, Tsagakis K, Marggraf G, Kamler M, et al. Prognostic value of preoperative cardiac troponin I in patients undergoing emergency coronary artery bypass surgery with non-ST-elevation or ST-elevation acute coronary syndromes. *Circulation.* 2006;114(1 Suppl):I448-53.

119. Nagurney JT, Brown DF, Chae C, Chang Y, Chung WG, Cranmer H, et al. The sensitivity of cardiac markers stratified by symptom duration. *The Journal of Emergency Medicine.* 2005;29(4):409-15.

120. Crescenzi G, Cedrati V, Landoni G, Scandroglio AM, Bignami E, Bove T, et al. Cardiac biomarker release after CABG with different surgical techniques. *Journal of Cardiothoracic and Vascular Anesthesia.* 2004;18(1):34-7.

121. Lurati Buse GA, Koller MT, Grapow M, Bolliger D, Seeberger M, Filipovic M. The prognostic value of troponin release after adult cardiac surgery - a meta-analysis. *European Journal of Cardio-Thoracic surgery : official journal of the European Association for Cardio-Thoracic Surgery.* 2010;37(2):399-406.

122. Rubini Gimenez M, Twerenbold R, Reichlin T, Wildi K, Haaf P, Schaefer M, et al. Direct comparison of high-sensitivity-cardiac troponin I vs. T for the early diagnosis of acute myocardial infarction. *European Heart Journal.* 2014;35(34):2303-11.

123. Haaf P, Reichlin T, Twerenbold R, Hoeller R, Rubini Gimenez M, Zellweger C, et al. Risk stratification in patients with acute chest pain using three high-sensitivity cardiac troponin assays. *European Heart Journal.* 2014;35(6):365-75.

124. Wijeysundera DN, Bender JS, Beattie WS. Alpha-2 adrenergic agonists for the prevention of cardiac complications among patients undergoing surgery. *Cochrane Database Systematic Review.* 2009(4). DOI: 10.1002/14651858.CD004126.pub2.

125. Aronson S, Dyke CM, Levy JH, Cheung AT, Lumb PD, Avery EG, et al. Does Perioperative Systolic Blood Pressure Variability Predict Mortality After Cardiac Surgery? An Exploratory Analysis of the ECLIPSE trials. *Anesthesia and Analgesia.* 2011;113(1):19-30.

126. Franke A, Lante W, Fackeldey V, Becker HP, Kurig E, Zöller LG, et al. Pro-inflammatory cytokines after different kinds of cardio-thoracic surgical procedures: is what we see what we know? *European Journal of Cardio-Thoracic Surgery.* 2005;28(4):569-75.

127. Ji B, Liu J. Myocardial protection during heart surgery in China. *China Medical Journal (Engl).* 2007;120(1):62-7.

128. Chew MS. Does modified ultrafiltration reduce the systemic inflammatory response to cardiac surgery with cardiopulmonary bypass? *Perfusion.* 2004;19 Suppl 1:S57-60.

129. Chew MS, Brandslund I, Brix-Christensen V, Ravn HB, Hjortdal VE, Pedersen J, et al. Tissue injury and the inflammatory response to pediatric cardiac surgery with cardiopulmonary bypass: a descriptive study. *Anesthesiology.* 2001;94(5):745-53; discussion 5A.

130. Visser L, Zuurbier CJ, Hoek FJ, Opmeer BC, de Jonge E, de Mol BAJM, et al. Glucose, insulin and potassium applied as perioperative hyperinsulinaemic normoglycaemic clamp: effects on inflammatory response during coronary artery surgery. *British Journal of Anaesthesia.* 2005;95(4):448-57.

131. Chew MS, Brix-Christensen V, Ravn HB, Brandslund I, Ditlevsen E, Pedersen J, et al. Effect of modified ultrafiltration on the inflammatory response in paediatric open-heart surgery: a prospective, randomized study. *Perfusion-Uk.* 2002;17(5):327-33.

132. Kanemoto S, Matsubara M, Noma M, Leshnower BG, Parish LM, Jackson BM, et al. Mild Hypothermia to Limit Myocardial Ischemia-Reperfusion Injury: Importance of Timing. *Annals of Thoracic Surgery.* 2009;87(1):157-63.

133. Ji B, Feng Z, Liu J, Long C. Myocardial protection related to magnesium content of cold blood hyperkalemic cardioplegic solutions in CABG. *The Journal of Extra-Corporeal Technology.* 2002;34(2):107-10.

134. Ye J, Sun JK, Hoffenberg EF, Shen J, Yang LJ, Summers R, et al. Does retrograde warm blood cardioplegic perfusion provide better protection of ischemic areas than antegrade warm blood cardioplegic perfusion? A magnetic resonance study in pig hearts. *Journal of Thoracic and Cardiovascular Surgery.* 1999;117(5):994-1003.

135. Jian W, Su L, Yiwu L. The effects of magnesium prime solution on magnesium levels and potassium loss in open heart surgery. *Anesthesia and Analgesia.* 2003;96(6):1617-20, table of contents.

136. Raja SG, Dreyfus GD. Modulation of systemic inflammatory response after cardiac surgery. *Asian Cardiovascular & Thoracic Annals.* 2005;13(4):382-95.

137. Corcoran TB, Engel A, Sakamoto H, O'Shea A, O'Callaghan-Enright S, Shorten GD. The effects of propofol on neutrophil function, lipid peroxidation and inflammatory response during elective coronary artery bypass grafting in patients with impaired ventricular function. *British Journal of Anaesthesia.* 2006;97(6):825-31.

138. Laffey JG, Boylan JF, Cheng DCH. The systemic inflammatory response to cardiac surgery: implications for the anesthesiologist. *Anesthesiology*. 2002;97(1):215-52.

139. Loix S, De Kock M, Henin P. The anti-inflammatory effects of ketamine: state of the art. *Acta Anaesthesiologica Belgica.* 2011;62(1):47-58.

140. Peltoniemi MA, Hagelberg NM, Olkkola KT, Saari TI. Ketamine: A Review of Clinical Pharmacokinetics and Pharmacodynamics in Anesthesia and Pain Therapy. *Clinical Pharmacokinetics.* 2016.

141. Nishina K, Akamatsu H, Mikawa K, Shiga M, Maekawa N, Obara H, et al. The inhibitory effects of thiopental, midazolam, and ketamine on human neutrophil functions. *Anesthesia and Analgesia.* 1998;86(1):159-65.

142. Kim SN, Son SC, Lee SM, Kim CS, Yoo DG, Lee SK, et al. Midazolam inhibits proinflammatory mediators in the lipopolysaccharide-activated macrophage. *Anesthesiology.* 2006;105(1):105-10.

143. Bartosikova L, Necas J, Bartosik T, Frana P, Pavlik M. Changes in biomechanical parameters during heart perfusion and after midazolam pre-medication--experimental pilot study. *Biomed Papers of the Medical Faculty of the University of Palacky Olomouc Czech Republic.* 2008;152(1):79-82.

144. Symons JA, Myles PS. Myocardial protection with volatile anaesthetic agents during coronary artery bypass surgery: a meta-analysis. *British Journal of Anaesthesia.* 2006;97(2):127-36.

145. Tritapepe L, Landoni G, Guarracino F, Pompei F, Crivellari M, Maselli D, et al. Cardiac protection by volatile anaesthetics: a multicentre randomized controlled study in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass. *European Journal of Anaesthesia.* 2007;24(4):323-31.

146. Landoni G, Fochi O, Torri G. Cardiac protection by volatile anaesthetics: A review. *Current Vascular Pharmacology.* 2008;6(2):108-11.

147. Yu CH, Beattie WS. The effects of volatile anesthetics on cardiac ischemic complications and mortality in CABG: a meta-analysis. *Canadian Journal of Anaesthesia.* 2006;53(9):906-18.

148. Landoni G, Lomivorotov V, Silvetti S, Nigro Neto C, Pisano A, Alvaro G, et al. Nonsurgical Strategies to Reduce Mortality in Patients Undergoing Cardiac Surgery: An Updated Consensus Process. *Journal of Cardiothoracic and Vascular Anesthesia.* 2018;32(1):225-35.

149. Dorman BH, Zucker JR, Verrier ED, Gartman DM, Slachman FN. Clonidine improves perioperative myocardial ischemia, reduces anesthetic requirement, and alters hemodynamic parameters in patients undergoing coronary artery bypass surgery. *Journal of Cardiothoracic and Vascular Anesthesia.* 1993;7(4):386-95.

150. Abi-Jaoude F, Brusset A, Ceddaha A, Schlumberger S, Raffin L, Dubois C, et al. Clonidine premedication for coronary artery bypass grafting under high-dose alfentanil anesthesia: intraoperative and postoperative hemodynamic study. *Journal of Cardiothoracic and Vascular Anesthesia.* 1993;7(1):35-40.

151. Myles PS, Hunt JO, Holdgaard HO, McRae R, Buckland MR, Moloney J, et al. Clonidine and cardiac surgery: Haemodynamic and metabolic effects, myocardial ischaemia and recovery. *Anaesthesia and Intensive Care.* 1999;27(2):137-47.

152. Bhana N, Goa KL, McClellan KJ. Dexmedetomidine. *Drugs.* 2000;59(2):263-8; discussion 9-70.

153. Afonso J, Reis F. Dexmedetomidine: current role in anesthesia and intensive care. *Revista Brasileira de Anestesiologia.* 2012;62(1):118-33.

154. Wagner D, Pasko D, Phillips K, Waldvogel J, Annich G. In vitro clearance of dexmedetomidine in extracorporeal membrane oxygenation. *Perfusion.* 2013;28(1):40-6.

155. Venn RM, Grounds RM. Comparison between dexmedetomidine and propofol for sedation in the intensive care unit: patient and clinician perceptions. *British Journal of Anaesthesia.* 2001;87(5):684-90.

156. Venn RM, Bryant A, Hall GM, Grounds RM. Effects of dexmedetomidine on adrenocortical function, and the cardiovascular, endocrine and inflammatory responses in post-operative patients needing sedation in the intensive care unit. *British Journal of Anaesthesia.* 2001;86(5):650-6.

157. Venn RM, Grounds RM. Comparison between dexmedetomidine and propofol for sedation in the intensive care unit: patient and clinician perceptions. *British Journal of Anaesthesia.* 2001;87(5):684-90.

158. Flacke WE, Flacke JW, Bloor BC, McIntee DF, Sagan M. Effects of dexmedetomidine on systemic and coronary hemodynamics in the anesthetized dog. *Journal of Cardiothoracic and Vascular Anesthesia.* 1993;7(1):41-9.

159. Okada H, Kurita T, Mochizuki T, Morita K, Sato S. The cardioprotective effect of dexmedetomidine on global ischaemia in isolated rat hearts. *Resuscitation.* 2007;74(3):538-45.

160. Mimuro S, Katoh T, Suzuki A, Yu S, Adachi YU, Uraoka M, et al. Deterioration of myocardial injury due to dexmedetomidine administration after myocardial ischaemia. *Resuscitation.* 2010;81(12):1714-7.

161. Roekaerts PM, Prinzen FW, De Lange S. Beneficial effects of dexmedetomidine on ischaemic myocardium of anaesthetized dogs. *British Journal of Anaesthesia.* 1996;77(3):427-9.

162. Kocoglu H, Karaaslan K, Gonca E, Bozdogan O, Gulcu N. Preconditionin effects of dexmedetomidine on myocardial ischemia/reperfusion injury in rats. *International Journal of Clinical and Experimental Medicine.* 2008;69(2):150-8.

163. Ibacache M, Sanchez G, Pedrozo Z, Galvez F, Humeres C, Echevarria G, et al. Dexmedetomidine preconditioning activates pro-survival kinases and attenuates regional ischemia/reperfusion injury in rat heart. *Biochimica et Biophysica Acta*. 2012;1822(4):537-45.

164. Talke P, Li J, Jain U, Leung J, Drasner K, Hollenberg M, et al. Effects of perioperative dexmedetomidine infusion in patients undergoing vascular surgery. The Study of Perioperative Ischemia Research Group. *Anesthesiology.* 1995;82(3):620-33.

165. Talke P, Chen R, Thomas B, Aggarwall A, Gottlieb A, Thorborg P, et al. The hemodynamic and adrenergic effects of perioperative dexmedetomidine infusion after vascular surgery. *Anesthesia and Analgesia.* 2000;90(4):834-9.

166. Ren J, Zhang H, Huang L, Liu Y, Liu F, Dong Z. Protective effect of dexmedetomidine in coronary artery bypass grafting surgery. *Experimental and Therapeutic Medicine.* 2013;6(2):497-502.

167. Lai YC, Tsai PS, Huang CJ. Effects of dexmedetomidine on regulating endotoxin-induced up-regulation of inflammatory molecules in murine macrophages. *The Journal of Surgical Research*. 2009;154(2):212-9.

168. Taniguchi T, Kurita A, Kobayashi K, Yamamoto K, Inaba H. Dose- and time-related effects of dexmedetomidine on mortality and inflammatory responses to endotoxin-induced shock in rats. *Journal of Anesthesia.* 2008;22(3):221-8.

169. Li B, Li Y, Tian S, Wang H, Wu H, Zhang A, et al. Anti-inflammatory Effects of Perioperative Dexmedetomidine Administered as an Adjunct to General Anesthesia: A Meta-analysis. *Scientific Reports.* 2015;5:12342.

170. Chen SL, Hua FZ, Lu J, Jiang Y, Tang YH, Tao L, et al. Effect of dexmedetomidine on myocardial ischemia-reperfusion injury. *International Journal of Clinical and Experimental Medicine.* 2015;8(11):21166-72.

171. Ueki M, Kawasaki T, Habe K, Hamada K, Kawasaki C, Sata T. The effects of dexmedetomidine on inflammatory mediators after cardiopulmonary bypass. *Anaesthesia.* 2014;69(7):693-700.

172. Farsad B. F JM, Totonchi Z, Gorjipour F, Omid S. O. . Effects of Dexmedetomidine on Surgical Stress Responses at Patients under CABG. *Biotech Research Asia*. 2016;13(3).

173. Franke A, Lante W, Fackeldey V, Becker HP, Kurig E, Zoller LG, et al. Pro-inflammatory cytokines after different kinds of cardio-thoracic surgical procedures: is what we see what we know? *European Journal of Cardio-Thoracic Surgery : official journal of the European Association for Cardio-thoracic Surgery.* 2005;28(4):569-75.

174. Ng RR, Chew ST, Liu W, Ong P, Caleb MG, Ti LK. The inflammatory response between miniaturised and conventional cardiopulmonary bypass after cardiac surgery in an Asian population. *Perfusion.* 2015;30(6):487-94.

175. Bical OM, Fromes Y, Gaillard D, Fischer M, Ponzio O, Deleuze P, et al. Comparison of the inflammatory response between miniaturized and standard CPB circuits in aortic valve surgery. *European Journal of Cardio-Thoracic Surgery : official journal of the European Association for Cardio-thoracic Surgery.* 2006;29(5):699-702.

176. Ren JJ, Zhang HJ, Huang LN, Liu Y, Liu FQ, Dong ZM. Protective effect of dexmedetomidine in coronary artery bypass grafting surgery. *Experimental and Therapeutic Medicine.* 2013;6(2):497-502.

177. Chi X, Liao M, Chen X, Zhao Y, Yang L, Luo A, et al. Dexmedetomidine Attenuates Myocardial Injury in Off-Pump Coronary Artery Bypass Graft Surgery. *Journal of Cardiothoracic and Vascular Anesthesia.* 2016;30(1):44-50.

178. Kim HJ, Kim WH, Kim G, Kim E, Park MH, Shin BS, et al. A comparison among infusion of lidocaine and dexmedetomidine alone and in combination in subjects undergoing coronary artery bypass graft: a randomized trial. *Contemporary Clinical Trials.* 2014;39(2):303-9.

179. Lee EH, Lee HM, Chung CH, Chin JH, Choi DK, Chung HJ, et al. Impact of intravenous lidocaine on myocardial injury after off-pump coronary artery surgery. *British Journal of Anaesthesia.* 2011;106(4):487-93.

180. Tosun Z, Baktir M, Kahraman HC, Baskol G, Guler G, Boyaci A. Does dexmedetomidine provide cardioprotection in coronary artery bypass grafting with cardiopulmonary bypass? A pilot study. *Journal of Cardiothoracic and Vascular Anesthesia.* 2013;27(4):710-5.

181. Riha H, Kotulak T, Brezina A, Hess L, Kramar P, Szarszoi O, et al. Comparison of the effects of ketamine-dexmedetomidine and sevoflurane-sufentanil anesthesia on cardiac biomarkers after cardiac surgery: an observational study. *Physiological Research / Academia Scientiarum Bohemoslovaca.* 2012;61(1):63-72.

182. Pai A, Heining M. Ketamine. *Continuing Education in Anaesthesia, Critical Care & Pain.* 2007;7(2):59-63.

183. Welters ID, Feurer MK, Preiss V, Muller M, Scholz S, Kwapisz M, et al. Continuous S-(+)-ketamine administration during elective coronary artery bypass graft surgery attenuates pro-inflammatory cytokine response during and after cardiopulmonary bypass. *British Journal of Anaesthesia.* 2011;106(2):172-9.

184. Neuhauser C, Preiss V, Feurer MK, Muller M, Scholz S, Kwapisz M, et al. Comparison of S-(+)-ketamine- with sufentanil-based anaesthesia for elective coronary artery bypass graft surgery: effect on troponin T levels. *British Journal of Anaesthesia.* 2008;100(6):765-71.

185. Salis S, Mazzanti VV, Merli G, Salvi L, Tedesco CC, Veglia F, et al. Cardiopulmonary bypass duration is an independent predictor of morbidity and mortality after cardiac surgery. *Journal of Cardiothoracic and Vascular Anesthesia.* 2008;22(6):814-22.

186. Al-Sarraf N, Thalib L, Hughes A, Houlihan M, Tolan M, Young V, et al. Cross-clamp time is an independent predictor of mortality and morbidity in low- and high-risk cardiac patients. *International Journal of Surgery.* 2011;9(1):104-9.

187. Oliveira EK, Turquetto AL, Tauil PL, Junqueira LF, Jr., Porto LG. Risk factors for prolonged hospital stay after isolated coronary artery bypass grafting. *Revista Brasileira de Cirurgia Cardiovascular : orgao oficial da Sociedade Brasileira de Cirurgia Cardiovascular.* 2013;28(3):353-63.

188. Cheng H, Li Z, Young N, Boyd D, Atkins Z, Ji F, et al. The Effect of Dexmedetomidine on Outcomes of Cardiac Surgery in Elderly Patients. *Journal of Cardiothoracic and Vascular Anesthesia*. 2016;30(6):1502-8.

189. Flacke WE, Flacke JW, Blow KD, McIntee DF, Bloor BC. Effect of dexmedetomidine, an alpha 2-adrenergic agonist, in the isolated heart. *Journal of Cardiothoracic and Vascular Anesthesia.* 1992;6(4):418-23.

190. Roekaerts PM, Prinzen FW, de Lange S. Coronary vascular effects of dexmedetomidine during reactive hyperemia in the anesthetized dog. *Journal of Cardiothoracic and Vascular Anesthesia.* 1996;10(5):619-26.

191. Chi X, Liao M, Chen X, Zhao Y, Yang L, Luo A, et al. Dexmedetomidine Attenuates Myocardial Injury in Off-Pump Coronary Artery Bypass Graft Surgery. *Journal of Cardiothoracic and Vascular Anesthesia.* 2016;30(1):44-50.

192. Tosun Z, Baktir M, Kahraman HC, Baskol G, Guler G, Boyaci A. Does Dexmedetomidine Provide Cardioprotection in Coronary Artery Bypass Grafting With Cardiopulmonary Bypass? A Pilot Study. *Journal of Cardiothoracic and Vascular Anesthesia.* 2013;27(4):710-5.

193. Patanwala AE, Erstad BL. Comparison of Dexmedetomidine Versus Propofol on Hospital Costs and Length of Stay. *Journal of Intensive Care Medicine.* 2016;31(7):466-70.

194. Kangasniemi OP, Biancari F, Luukkonen J, Vuorisalo S, Satta J, Pokela R, et al. Preoperative C-reactive protein is predictive of long-term outcome after coronary artery bypass surgery. *European Journal of Cardio-Thoracic Surgery : official journal of the European Association for Cardio-thoracic Surgery.* 2006;29(6):983-5.

195. Young YR, Sheu BF, Li WC, Hsieh TM, Hung CW, Chang SS, et al. Predictive value of plasma brain natriuretic peptide for postoperative cardiac complications--a systemic review and meta-analysis. *Journal of Critical Care.* 2014;29(4):696 e1-10.

196. Kocak EF, Kocak C, Aksoy A, Isiklar OO, Akcilar R, Ozdomanic IF, et al. High-sensitivity cardiac troponin T is more helpful in detecting peri-operative myocardial injury and apoptosis during coronary artery bypass graft surgery. *Cardiovascular Journal of Africa.* 2015;26(6):234-41.

197. Petaja L, Rosjo H, Mildh L, Suojaranta-Ylinen R, Kaukonen KM, Jokinen JJ, et al. Predictive value of high-sensitivity troponin T in addition to EuroSCORE II in cardiac surgery. *Interactive Cardiovascular and Thoracic Surgery.* 2016;23(1):133-41.

198. Eigel P, van Ingen G, Wagenpfeil S. Predictive value of perioperative cardiac troponin I for adverse outcome in coronary artery bypass surgery. *European Journal of Cardio-Thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery.* 2001;20(3):544-9.

199. Corsi DJ, Subramanian SV, Chow CK, McKee M, Chifamba J, Dagenais G, et al. Prospective Urban Rural Epidemiology (PURE) study: Baseline characteristics of the household sample and comparative analyses with national data in 17 countries. *American Heart Journal.* 2013;166(4):636-46.e4.

200. Dehghan M, Mente A, Zhang X, Swaminathan S, Li W, Mohan V, et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. *Lancet.* 2017;390(10107):2050-62.

201. Seftel HCKM. Myocardial infarction in Johannesburg Bantu. *South Afrrican Medical Journal.* 1970;44(1):8 – 12. [Internet]. [cited 2016Nov1]. Available from: https://wwwresearchgatenet/publication/17756423.

202. Schrire V. Heart disease in Southern Africa with special reference to ischaemic heart disease. *South African Medical Journal.* 1971;45(23):634 – 44. [Internet]. [cited 2016Nov1]. Available from: https://wwwresearchgatenet/publication/17627335.

203. Seedat YK. Risk factors leading to coronary heart disease among the Black, Indian and White population of Durban, South Africa. [Internet]. XVIII World congress of cardiology; 1998. [cited 2016Nov1]. Available from::https://wwwresearchgatenet/publication/281589651.

204. Tibazarwa K, Ntyinyane L, Sliwa K, Gerntholtz T, Wilkinson D, Stewart S. Profile and high prevalence of cardiovascular risk factors in an urban black african population: Update on heart awareness days in soweto. *South African Medical Journal.* 2007;97(11):1106-7.

205. Seedat YK. Ethnicity, hypertension, coronary heart disease and renal diseases in South Africa. *Ethnicity and Health.* 1996;1(4):349-57.

206. Chris Isles FJM. Low mortality from ischaemic heart disease among urban Blacks in South Africa. *Journal of Clinical Hypertension.* 1988;3(4):749-56.

207. Isles C, Lowe GD, Rankin BM, Forbes CD, Lucie N, Lever AF, et al. Abnormal haemostasis and blood viscosity in malignant hypertension. *Thrombosis and Haemostasis.* 1984;52(3):253-5.

208. Sigola LB, Adewuyi JO. Ethnicity, haemostasis and cardiovascular disease: the evidence from Africa. *Central African Journal of Medicine.* 1992;38(9):385-91.

209. Muszkat M, Sofowora GG, Wood AJ, Stein CM. Alpha2-adrenergic receptor-induced vascular constriction in blacks and whites. *Hypertension.* 2004;43(1):31-5.

210. Kurnik D, Muszkat M, Sofowora GG, Friedman EA, Dupont WD, Scheinin M, et al. Ethnic and genetic determinants of cardiovascular response to the selective alpha 2-adrenoceptor agonist dexmedetomidine. *Hypertension.* 2008;51(2):406-11.

211. Tellor BR, Arnold HM, Micek ST, Kollef MH. Occurrence and predictors of dexmedetomidine infusion intolerance and failure. *Hospital Practice.* (1995). 2012;40(1):186-92.

212. Yagar S, Yavas S, Karahalil B. The role of the ADRA2A C1291G genetic polymorphism in response to dexmedetomidine on patients undergoing coronary artery surgery. *Molecular Biology Reports.* 2011;38(5):3383-9.

213. Lang CC, Stein CM, He HB, Belas FJ, Blair IA, Wood M, et al. Blunted blood pressure response to central sympathoinhibition in normotensive blacks: increased importance of nonsympathetic factors in blood pressure maintenance in blacks. *Hypertension.* 1997;30(2 Pt 1):157-62.

214. Iirola T, Ihmsen H, Laitio R, Kentala E, Aantaa R, Kurvinen JP, et al. Population pharmacokinetics of dexmedetomidine during long-term sedation in intensive care patients. *British Journal of Anaesthesia.* 2012;108(3):460-8.

215. Iirola T, Laitio R, Kentala E, Aantaa R, Kurvinen JP, Scheinin M, et al. Highly variable pharmacokinetics of dexmedetomidine during intensive care: a case report. *Journal of Medical Case Reports.* 2010;4:73.

216. American Society of Anesthesiologists Task Force on Perioperative Blood M. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management*. *Anesthesiology.* 2015;122(2):241-75.

217. ROCHE.COM. Elecsys® Troponin T high sensitive (TnT-hs). [Internet]. [Cited 2016 Oct3]. Availble from: http://wwwcobascom/home/product/clinical-and-immunochemistry-testing/elecsys-troponin-t-hs-tnt-hshtml.

218. ROCHE. Cardiac C-Reactive Protein (Latex) High Sensitive. [Internet]. [Cited 2016 Oct3]. Availble from: https://usdiagnosticsrochecom/products/04628918190/PARAM2640/overlayhtml.

219. Solutions RC. NT-proBNP. [Internet]. [Cited 2016 Oct3]. Availble from: https://usdiagnosticsrochecom/en/crc_nt-probnp_summary_contenthtml.

220. Eurodiacnostico. ELIZA test. [Internet]. [Cited 2016 Oct3]. Availble from: http://wwweurodiagnosticocom/en/assay-kits/elisa-kitshtml.

221. Freund Y, Chenevier-Gobeaux C, Bonnet P, Claessens YE, Allo JC, Doumenc B, et al. High-sensitivity versus conventional troponin in the emergency department for the diagnosis of acute myocardial infarction. *Critical Care*. 2011;15(3):R147.

222. Kundra TS, Kaur P. Effect of Dexmedetomidine on Normal Coronary Vessel Diameter. *Pharmacology*. 2016;98(5-6):217-9.

223. Kundra TS, Nagaraja PS, Singh NG, Dhananjaya M, Sathish N, Manjunatha N. Effect of dexmedetomidine on diseased coronary vessel diameter and myocardial protection in percutaneous coronary interventional patients. *Annals of Cardiac Anaesthesia.* 2016;19(3):394-8.

224. Chen Q, Wu W, Zhang GC, Cao H, Chen LW, Hu YN, et al. Dexmedetomidine attenuates hypoxemia during palliative reconstruction of the right ventricular outflow tract in pediatric patients. *Medicine.* 2014;93(13):e69.

225. Jones GM, Murphy CV, Gerlach AT, Goodman EM, Pell LJ. High-dose dexmedetomidine for sedation in the intensive care unit: an evaluation of clinical efficacy and safety. *Annals of Pharmacotherapy.* 2011;45(6):740-7.

226. Chorney SR, Gooch ME, Oberdier MT, Keating D, Stahl RF. The safety and efficacy of dexmedetomidine for postoperative sedation in the cardiac surgery intensive care unit. *HSR Proceedings in Intensive Care & Cardiovascular Anesthesia*. 2013;5(1):17-24.

227. Tosun Z, Baktir M, Kahraman HC, Baskol G, Guler G, Boyaci A. Does dexmedetomidine provide cardioprotection in coronary artery bypass grafting with cardiopulmonary bypass? A pilot study. *Journal of Cardiothoracic and Vascular Anesthesia.* 2013;27(4):710-5.

228. Riha H, Kotulak T, Brezina A, Hess L, Kramar P, Szarszoi O, et al. Comparison of the effects of ketamine-dexmedetomidine and sevoflurane-sufentanil anesthesia on cardiac biomarkers after cardiac surgery: an observational study. *Physiological research / Academia Scientiarum Bohemoslovaca.* 2012;61(1):63-72.

229. Michalopoulos A, Tzelepis G, Pavlides G, Kriaras J, Dafni U, Geroulanos S. Determinants of duration of ICU stay after coronary artery bypass graft surgery. *British Journal of Anaesthesia.* 1996;77(2):208-12.

230. G King RN. Why Propensity Scores Should Not Be Used for Matching. [Internet]. [Cited 2016Nov10]. Available from: http://j.mp/2ovYGsW.

231. Maldonado JR, Wysong A, van der Starre PJ, Block T, Miller C, Reitz BA. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. *Psychosomatics.* 2009;50(3):206-17.

232. Balkanay OO, Goksedef D, Omeroglu SN, Ipek G. The dose-related effects of dexmedetomidine on renal functions and serum neutrophil gelatinase-associated lipocalin values after coronary artery bypass grafting: a randomized, triple-blind, placebo-controlled study. *Interactive Cardiovascular and Thoracic Surgery*. 2015;20(2):209-14.

233. Pasin L, Greco T, Feltracco P, Vittorio A, Neto CN, Cabrini L, et al. Dexmedetomidine as a Sedative Agent in Critically Ill Patients: A Meta-analysis of Randomized Controlled Trials. *Public Library of Science One*. 2013;8(12).

234. Khalil MA, Abdel Azeem MS. The impact of dexmedetomidine infusion in sparing morphine consumption in off-pump coronary artery bypass grafting. *Seminars in Cardiothoracic and Vascular Anesthesia*. 2013;17(1):66-71.

235. Hill S. Pharmacokinetics of drug infusions. *Continued Education in Anaesthesia, Critical Care and Pain*. (2004) 4 (3): 76-80. 2004.

236. Herr DL, Sum-Ping STJ, England M. ICU sedation after coronary artery bypass graft surgery: dexmedetomidine-based versus propofol-based sedation regimens. *Journal of Cardiothoracic and Vascular Anesthesia.* 2003;17(5):576-84.

237. Park JB, Bang SH, Chee HK, Kim JS, Lee SA, Shin JK. Efficacy and safety of dexmedetomidine for postoperative delirium in adult cardiac surgery on cardiopulmonary bypass. *The Korean Journal of Thoracic and Cardiovascular Surgery.* 2014;47(3):249-54.

238. Tan JA, Ho KM. Use of dexmedetomidine as a sedative and analgesic agent in critically ill adult patients: a meta-analysis. *Intensive Care Medicine.* 2010;36(6):926-39.

239. Geng J, Qian J, Cheng H, Ji F, Liu H. The Influence of Perioperative Dexmedetomidine on Patients Undergoing Cardiac Surgery: A Meta-analysis. *Public Library of Science One.* 2016;11(4):e0152829.

240. Williams TA, Ho KM, Dobb GJ, Finn JC, Knuiman M, Webb SA, et al. Effect of length of stay in intensive care unit on hospital and long-term mortality of critically ill adult patients. *British Journal of Anaesthesia.* 2010;104(4):459-64.

241. Kramer AA, Zimmerman JE. The relationship between hospital and intensive care unit length of stay. *Critical Care Medicine.* 2011;39(5):1015-22.

242. Pathan H, Williams J. Basic opioid pharmacology: an update. *British Journal of Pain.* 2012;6(1):11-6.

243. Brandao PG, Lobo FR, Ramin SL, Sakr Y, Machado MN, Lobo SM. Dexmedetomidine as an Anesthetic Adjuvant in Cardiac Surgery: a Cohort Study. *Brazilian Journal of Cardiovascular Surgery.* 2016;31(3):213-8.

244. Park JH, Kwon JY. Remifentanil or dexmedetomidine for monitored anesthesia care during cataract surgery under topical anesthesia. *Korean Journal of Anesthesiology.* 2012;63(1):92-3.

245. Xue F-S, Wang S-Y, Cui X-L, Li R-P. Does perioperative dexmedetomidine improve mortality after coronary artery bypass surgery? *Journal of Cardiothoracic and Vascular Anesthesia.* 2014;28(5):e46-7.

246. Christenson JT, Simonet F, Schmuziger M. The influence of age on the outcome of primary coronary artery bypass grafting. *The Journal of Cardiovascular Surgery*. 1999;40(3):333-8.

247. Michel P, Roques F, Nashef SA, Euro SPG. Logistic or additive EuroSCORE for high-risk patients? *European Journal of Cardio-Thoracic Surgery : official journal of the European Association for Cardio-thoracic Surgery.* 2003;23(5):684-7.

248. Deborah S. Wagner PD, and Chad M. Brummett, MD. Dexmedetomidine: as safe as safe can be. *Seminars in Anesthesia, Perioperative Medicine and Pain*. (2006) 25, 77-83.

249. Kunisawa T, Ueno M, Kurosawa A, Nagashima M, Hayashi D, Sasakawa T, et al. Dexmedetomidine can stabilize hemodynamics and spare anesthetics before cardiopulmonary bypass. *Journal of Anesthesia.* 2011;25(6):818-22.

250. Martinez-Rumayor AA, de Lemos JA, Rohatgi AK, Ayers CR, Powell-Wiley TM, Lakoski SG, et al. Addition of highly sensitive troponin T and N-terminal pro-B-type natriuretic peptide to electrocardiography for detection of left ventricular hypertrophy: results from the Dallas Heart Study. *Hypertension.* 2013;61(1):105-11.

251. Duceppe E, Parlow J, MacDonald P, Lyons K, McMullen M, Srinathan S, et al. Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery. *The Canadian Journal of Cardiology.* 2017;33(1):17-32.

252. Zimmerman MA, Selzman CH, Cothren C, Sorensen AC, Raeburn CD, Harken AH. Diagnostic implications of C-reactive protein. *Archives of Surgery-Chicago.* 2003;138(2):220-4.

253. de Winter RJ. C-Reactive Protein and cardiac troponin for early risk stratification in patients with acute coronary syndromes. *Clinica Chimica Acta; International Journal of Clinical Chemistry*. 2001;311(1):53-6.

254. Rodseth RN. B type natriuretic peptide--a diagnostic breakthrough in peri-operative cardiac risk assessment? *Anaesthesia.* 2009;64(2):165-78.

255. Toss H, Lindahl B, Siegbahn A, Wallentin L. Prognostic influence of increased fibrinogen and C-reactive protein levels in unstable coronary artery disease. *Circulation.* 1997;96(12):4204-10.

256. Wang TJ, Gona P, Larson MG, Tofler GH, Levy D, Newton-Cheh C, et al. Multiple biomarkers for the prediction of first major cardiovascular events and death. *New Englland Journal of Medicine.* 2006;355(25):2631-9.

257. Tello-Montoliu A, Marin F, Roldan V, Mainar L, Lopez MT, Sogorb F, et al. A multimarker risk stratification approach to non-ST elevation acute coronary syndrome: implications of troponin T, CRP, NT pro-BNP and fibrin D-dimer levels. *Journal of Internal Medicine*. 2007;262(6):651-8.

258. Smedsrud MK, Gravning J, Omland T, Eek C, Morkrid L, Skulstad H, et al. Sensitive cardiac troponins and N-terminal pro-B-type natriuretic peptide in stable coronary artery disease: correlation with left ventricular function as assessed by myocardial strain. *International Journal of Cardiovascular Imaging*. 2015;31(5):967-73.

259. Biancari F, Lahtinen J, Lepojarvi S, Rainio P, Salmela E, Pokela R, et al. Preoperative C-reactive protein and outcome after coronary artery bypass surgery. *The Annals of Thoracic Surgery*. 2003;76(6):2007-12.

260. van Straten AHM, Hamad MAS, van Zundert AJ, Martens EJ, Schonberger JPAM, de Wolf AM. Preoperative C-reactive protein levels to predict early and late mortalities after coronary artery bypass surgery: Eight years of follow-up. *Journal of Thoracic And Cardiovascular Surgery.* 2009;138(4):954-8.

261. Lyon WJ, Baker RA, Andrew MJ, Tirimacco R, White GH, Knight JL. Relationship between elevated preoperative troponin T and adverse outcomes following cardiac surgery. *Australian and New Zealand Journal of Surgery*. 2003;73(1-2):40-4.

262. Gossl M, Yoon MH, Choi BJ, Rihal C, Tilford JM, Reriani M, et al. Accelerated coronary plaque progression and endothelial dysfunction: serial volumetric evaluation by IVUS. *Journal of The American College of Cardiology Cardiovascular Imaging*. 2014;7(1):103-4.

263. Liu H, Wang C, Liu L, Zhuang Y, Yang X, Zhang Y. Perioperative application of N-terminal pro-brain natriuretic peptide in patients undergoing cardiac surgery. *Journal of Cardiothoracic Surgery.* 2013;8:1.

264. Doenst T, Borger MA, Weisel RD, Yau TM, Maganti M, Rao V. Relation between aortic cross-clamp time and mortality - not as straightforward as expected. *European Journal of Cardio-Thoracic Surgery.* 2008;33(4):660-5.

265. Azarfarin R, Ashouri N, Totonchi Z, Bakhshandeh H, Yaghoubi A. Factors influencing prolonged ICU stay after open heart surgery. *Research in Cardiovascular Medicine*. 2014;3(4):e20159.

266. Williams JC, Klein TW, Goldberger BA, Sleasman JW, Mackman N, Goodenow MM. Delta(9)-Tetrahydrocannabinol (THC) enhances lipopolysaccharide-stimulated tissue factor in human monocytes and monocyte-derived microvesicles. *Journal of Inflammation.* 2015;12:39.

267. Almashrafi A, Alsabti H, Mukaddirov M, Balan B, Aylin P. Factors associated with prolonged length of stay following cardiac surgery in a major referral hospital in Oman: a retrospective observational study. *British Medical Journal – Open*. 2016;6(6):e010764.

268. Wang W, Bagshaw SM, Norris CM, Zibdawi R, Zibdawi M, MacArthur R, et al. Association between older age and outcome after cardiac surgery: a population-based cohort study. *Journal of Cardiothoracic Surgery.* 2014;9:177.

269. Barry DJ, El-Khuffash A, Molloy EJ. Elevated troponin and NT-ProBNP are associated with severe intraventricular haemorrhage in pre term infants. *Acta Paediatrica.* 2007;96:17-8.

270. Rodseth RN, Biccard BM, Chu R, Lurati Buse GA, Thabane L, Bakhai A, et al. Postoperative B-type natriuretic peptide for prediction of major cardiac events in patients undergoing noncardiac surgery: systematic review and individual patient meta-analysis. *Anesthesiology.* 2013;119(2):270-83.

271. Thielmann M, Massoudy P, Marggraf G, Knipp S, Schmermund A, Piotrowski J, et al. Role of troponin I, myoglobin, and creatine kinase for the detection of early graft failure following coronary artery bypass grafting. *European Journal of Cardio-Thoracic Surgery : official journal of the European Association for Cardio-thoracic Surgery.* 2004;26(1):102-9.

272. Nesher N, Alghamdi AA, Kumar P, Sever JY, Moussa F, Christakis GT, et al. Troponin after cardiac surgery; A predictor or a phenomenon? *Circulation.* 2006;114(18):475-.

273. Crescenzi G, Cedrati V, Landoni G, Scandroglio AM, Bignami E, Bove T, et al. Cardiac biomarker release after CABG with different surgical techniques. *Journal of Cardiothoracic and Vascular Anesthesia.* 2004;18(1):34-7.

274. Body mass index – WHO. [Internet]. [Cited 2016Nov16]. Availale from: http://appswhoint/bmi/indexjsp?introPage=intro_3html.

275. Ortega VE, Meyers DA. Pharmacogenetics: implications of race and ethnicity on defining genetic profiles for personalized medicine. *Journal of Allergy and Clinical Immunology*. 2014;133(1):16-26.

276. Albert MA. Heart failure in the urban African enclave of Soweto: a case study of contemporary epidemiological transition in the developing world. *Circulation.* 2008;118(23):2323-5.

277. Chesler E, Mitha AS, Weir EK, Matisonn RE, Hitchcock PJ. Myocardial infarction in the black population of South Africa: coronary arteriographic findings. *American Heart Journal.* 1978;95(6):691-6.

278. Stewart S, Libhaber E, Carrington M, Damasceno A, Abbasi H, Hansen C, et al. The clinical consequences and challenges of hypertension in urban-dwelling black Africans: insights from the Heart of Soweto Study. *International Journal of Cardiology.* 2011;146(1):22-7.

279. Stewart S, Carrington MJ, Pretorius S, Ogah OS, Blauwet L, Antras-Ferry J, et al. Elevated risk factors but low burden of heart disease in urban African primary care patients: a fundamental role for primary prevention. *International Journal of Cardiology.* 2012;158(2):205-10.

280. Opie LH, Seedat YK. Hypertension in sub-Saharan African populations. *Circulation.* 2005;112(23):3562-8.

281. Stalls CM, Triplette MA, Viera AJ, Pathman DE, Cohen MG, Rossi JS. The association between body mass index and coronary artery disease severity: a comparison of black and white patients. *American Heart Journal.* 2014;167(4):514-20.

282. Omar MA, Seedat MA, Motala AA, Dyer RB, Becker P. The prevalence of diabetes mellitus and impaired glucose tolerance in a group of urban South African blacks. *South African Medical Journal*. 1993;83(9):641-3.

283. Bateman C. Izindaba – Motsoaledi declares war on disease-causing products. *South African Medical Journal*. 2011;101(8): 503 – 504

284. O'Donnell PH, Dolan ME. Cancer pharmacoethnicity: ethnic differences in susceptibility to the effects of chemotherapy. *Clinical Cancer Research : an official journal of the American Association for Cancer Research.* 2009;15(15):4806-14.

285. Roekaerts PM, Lawrence CJ, Prinzen FW, de Lange S. Alleviation of the peripheral hemodynamic effects of dexmedetomidine by the calcium channel blocker isradipine. *Acta Anaesthesiologica Scandinavica.* 1997;41(3):364-70.

286. Kocoglu H, Alan C, Cakir DU, Malkoc E, Cosansu K, Kirilmaz B, et al. Association between serum inhibin-B levels and coronary artery disease in aging males. *Archives of Medical Science* : AMS. 2013;9(5):796-801.

287. Chi XH, Liao MF, Chen X, Zhao YL, Yang L, Luo AL, et al. Dexmedetomidine Attenuates Myocardial Injury in Off-Pump Coronary Artery Bypass Graft Surgery. Journal of cardiothoracic and vascular anesthesia. 2016;30(1):44-50.

288. Hozo S, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BioMed Central Medical Research Methodology* [Internet]. 2005; 5(1):[13 p.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcmr/articles/CMR-9915/frame.html.

289. Ammar A, Mahmoud K, Kasemy Z, Helwa M. Cardiac and renal protective effects of dexmedetomidine in cardiac surgeries: A randomized controlled trial. *Saudi journal of anaesthesia.* 2016;10(4):395-401.

290. Soliman R, Hussien M. Comparison of the renoprotective effect of dexmedetomidine and dopamine in high-risk renal patients undergoing cardiac surgery: a double-blind randomized study. *Annals of cardiac anaesthesia* [Internet]. 2017; 20(4):[408-15 pp.]. Available from: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/987/CN-01430987/frame.html.

291. Li X, Yang J, Nie XL, Zhang Y, Li XY, Li LH, et al. Impact of dexmedetomidine on the incidence of delirium in elderly patients after cardiac surgery: A randomized controlled trial. *Public Library of Science One*. 2017;12(2):e0170757.

292. Cho JS, Shim JK, Soh S, Kim MK, Kwak YL. Perioperative dexmedetomidine reduces the incidence and severity of acute kidney injury following valvular heart surgery. *Kidney international*. 2016;89(3):693-700.

293. Huang J, Liu W, Zhan Y, Hou B, Chen S. The effects of dexmedetomidine on inflammatory responses in patients undergoing valve replacement surgery with cardiopulmonary bypass. *International journal of clinical and experimental medicine.* 2017;10(4):6482-8.

294. Khalil MA, Abdel Azeem MS. The impact of dexmedetomidine infusion in sparing morphine consumption in off-pump coronary artery bypass grafting. *Seminars in cardiothoracic and vascular anesthesia.* 2013;17(1):66-71.

295. Zhang JZW. Effects of dexmedetomidine on inflammatory responses in patients undergoing cardiac valve replacement with cardiopulmonary bypass / 中华麻醉学杂志. *Chinese Journal of Anesthesiology.* 2013;33(10):1188-91.

296. Wang Z, Chen Q, Guo H, Li Z, Zhang J, Lv L, et al. Effects of dexmedetomidine on H-FABP, CKMB, cTnI levels, neurological function and near-term prognosis in patients undergoing heart valve replacement. *Experimental and Therapeutic Medicin*e. 2017;14(6):5851-6.

297. Türktan M, Güneş Y, Yaliniz H, Matyar S, Hatipoğlu Z, Güleç E, et al. Comparison of the cardioprotective effects of dexmedetomidine and remifentanil in cardiac surgery. *Turkish Journal of Medical Science.* 2017;47(5):1403-9.

298. Liu Y, Sheng B, Wang S, Lu F, Zhen J, Chen W. Dexmedetomidine prevents acute kidney injury after adult cardiac surgery: A meta-analysis of randomized controlled trials. *BioMed Central Anesthesiology.* 2018;18(1).

299. Gong Z, Ma L, Zhong YL, Li J, Lv J, Xie YB. Myocardial protective effects of dexmedetomidine in patients undergoing cardiac surgery: A meta-analysis and systematic review. *Experimental and Therapeutic Medicine.* 2017;13(5):2355-61.

300. Chen X, Huang T, Cao X, Xu G. Comparative Efficacy of Drugs for Preventing Acute Kidney Injury after Cardiac Surgery: A Network Meta-analysis. *American Journal of Cardiovascular Drugs.* 2018;18(1):49-58.

301. Yang GZ, Xue FS, Liu YY. Use of a meta-analysis to assess the preventive effect of dexmedetomidine on cardiac surgery-associated acute kidney injury. *Critical care.* 2018;22(1):85.

302. Liu H, Ji F, Peng K, Applegate RL, 2nd, Fleming N. Sedation After Cardiac Surgery: Is One Drug Better Than Another? *Anesthesia and Analgesia.* 2017;124(4):1061-70.

303. Melsen WG, Bootsma MC, Rovers MM, Bonten MJ. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases.* 2014;20(2):123-9.

304. Consort 2010 – Consort Statement. [Internet]. [Cited 2017 May11]. Available from: http://www.consort-statement.org/consort-2010.

APPENDICES

Appendix 1: Medicines Control Council

09/07/2013 09:48 0123958775 CEAT PAGE 01/01

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

MEDICINES CONTROL COUNCIL
The Registrar of Medicines, Private Bag X828, PRETORIA, 0001
Tel 012 395 8000 Fax 012 395 9201
Tel: Inquiries:
Fax: Reference:

FAX AND MAIL TO:

Dr P Motshabi
Department of Anaesthesia
Chris Hani Baragwanath Hospital

MR PHILIP MABILLE
N2/19/8/2 (2703)
Datum * Date 09 July 2013
Tel: 0123958129
Fax: 0123958775

Fax: 0865270585

Dear Dr Motshabi,

PROTOCOL: M111179

TITLE: DEXMEDETOMIDINE IN CORONARY ARTERY BYPASS GRAFT SURGERY: EFFECTS ON MYOCARDIAL ISCHEMIC MARKERS, INFLAMMATORY MARKERS, INTENSIVE CARE UNIT AND HOSPITAL STAY

RE : ADDITIONAL CTC QUERIES

Study category 2A
1.Submit a complete exclusion criteria in the application form (page 16 of 3 CTF1 ,point F) which in edited form is incomplete.

Regards,

MR PHILIP MABILLE
FOR AND ON BEHALF OF REGISTRAR OF MEDICINES

ETHICS REFERENCE NO: 20130136

Page 1 of 1

Appendix 2: Human Research Ethics Committee

.UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Palesa Motshabi

CLEARANCE CERTIFICATE	M111179
PROJECT	D Dexmedetomidine during Coronary Artery Bypass Graft Surgery: Effects on Ischaemic and Inflammatory Markers, Mortality, Length Intensive Care Unit and Hospital Stay
INVESTIGATORS	Dr Palesa Motshabi
DEPARTMENT	Department of Anaesthesia
DATE CONSIDERED	25/11/2011
DECISION OF THE COMMITTEE*	Approed unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 11/09/2013 **CHAIRPERSON** .....
(Professor P E Cleaton Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr M Nethononda

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 3: Postgraduate Committee

Dear Dr Motshabi

I have pleasure in informing you that the title of your research has been approved. However, we are unable to send you the formal approval letter as it is system generated and our system is down until mid-January 2013. As soon as the letter is generated, it will be sent to you.

You may in the meantime, proceed with your research as long as you have obtained the Ethics Clearance.

You will be required to submit to the Faculty Office on submission of the report:

- PhD Three/Masters two bound copies of the Thesis/Research Report/dissertation
- An electronic copy in PDF format (name clearly labeled)
- Supervisor's clearance form, attached
- Submission form, see attached.
- Sign all copies of the form

Please note that you have to register every year until your graduation.

We wish you success with your research.

Regards

Ms Rosen Mhlongo

Postgraduate Faculty Officer Research

Postgraduate Office

Faculty of Health Sciences

University of the Witwatersrand

7 York Road, Parktown,

Johannesburg, South Africa

2193

Tel: +27 11 717 2125

Fax: +27 11 717 2119

Email:matshidiso.mhlongo@wits.ac.za

This communication is intended for the addressee only. It is confidential. If you have received this communication in error, please notify us immediately and destroy the original message. You may not copy or disseminate this communication without the permission of the University. Only authorized signatories are competent to enter into agreements on behalf of the University and recipients are thus advised that the content of this message may not be legally binding on the University and may contain the personal views and opinions of the author, which are not necessarily the views and opinions of The University of the Witwatersrand, Johannesburg. All agreements between the University and outsiders are subject to South African Law unless the University agrees in writing to the contrary.

Appendix 4: Title Change





16 August 2017
Person No. 8901284X
TAA

Dr PMV Motshabi
P O Box 524
Melrose Arch
Johannesburg
2076

Dear Dr Motshabi

Doctor of Philosophy: Change of title of research

I am pleased to inform you that the following change in title of your Thesis for the degree of Doctor of Philosophy has been approved:

From: Dexmedetomidine during coronary artery bypass graft surgery: Effects on myocardial ischaemic and inflammatory markers, mortality and length of intensive care unit and hospital stay

To: Impact of dexmedetomidine on postoperative biomarkers, length of hospitalization and mortality in patients undergoing coronary artery bypass graft surgery

Yours sincerely

_____
Miss Thando Mbolekwa
On behalf of Mrs Sandra Benn
Faculty Registrar

R14/49 Dr Palesa Motshabi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170985

NAME: (Principal Investigator)	Dr Palesa Motshabi
DEPARTMENT:	Anaesthesia Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Impact of Dexmedetomidine on Postoperative Biomakers, Length of Hospitalization and Mortality in Patients undergoing Coronary Artery Bypass Graft Surgery
DATE CONSIDERED:	25/11/2011 (Initial Application)
DECISION:	Approved unconditionally
CONDITIONS:	Renewal for 5 Years Valid for the Period 01 October 2017 - 31 October 2022 (Previously M111179) Final Approval 11/09/2013 (delayed due to MCC Approval)
SUPERVISOR:	Prof M Nethononda
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	20/10/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially review September and will therefore be due in the month of September each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 20/10/17

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 5: Information leaflet and informed consent

APPENDIX 5 : INFORMATION LEAFLET AND INFORMED CONSENT

Each PARTICIPANT must receive, read and understand this document

before any study-related procedure

STUDY NUMBER :

STUDY TITLE : **Dexmedetomidine during Coronary Artery Bypass Graft Surgery: Effects on myocardial ischaemic and inflammatory markers, mortality and length of intensive care unit and hospital stay.**

SPONSOR :

INVESTIGATOR : Dr Palesa Motshabi

INSTITUTION : University of the Witwatersrand

DAYTIME AND AFTERHOURS TELEPHONE NUMBER **: 0834321994**

To the potential Participant: *This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home* ***an unsigned copy of this consent*** *form to think about or discuss with family or friends* ***before making your decision.***

A. Protocol …….. English Informed Consent
B. Version 1……. (Dated 05/08/2012)
C. Investigator's name : Dr Palesa Motshabi
D. Approved by Wits HREC
E. Date approved: …/……../…….

Participant Initials: ____ ____ __

Participant Number: _____

REF: SOP
Version:

APPENDIX 5 : INFORMATION LEAFLET AND INFORMED CONSENT

Each PARTICIPANT must receive, read and understand this document

before any study-related procedure

STUDY NUMBER :

STUDY TITLE : **Dexmedetomidine during Coronary Artery Bypass Graft Surgery: Effects on myocardial ischaemic and inflammatory markers, mortality and length of intensive care unit and hospital stay.**

SPONSOR :

INVESTIGATOR : Dr Palesa Motshabi

INSTITUTION : University of the Witwatersrand

DAYTIME AND AFTERHOURS TELEPHONE NUMBER **: 0834321994**

To the potential Participant: *This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home* ***an unsigned copy of this consent*** *form to think about or discuss with family or friends* ***before making your decision.***

A. Protocol …….. English Informed Consent Participant Initials: ____ ____ __
B. Version 1……. (Dated 05/08/2012)
C. Investigator's name : Dr Palesa Motshabi
D. Approved by Wits HREC
E. Date approved: …/……../……. Participant Number: _____

REF: SOP
Version:

1. INTRODUCTION:

Good day, my name is PALESA MOTSHABI, I am a doctor at Chris Hani Baragwanath Academic Hospital and the Charlotte Maxeke Academic Hospital. I would like to *invite* you to consider participating in a research study, entitled: **Dexmedetomidine during Coronary Artery Bypass Graft Surgery: Effects on myocardial ischaemic and inflammatory markers, mortality and length of intensive care unit and hospital stay**

1. Before agreeing to participate, it is important that you read and understand the following explanation of the purpose of the study, the study procedures, benefits, risks, discomforts, and precautions as well as the alternative procedures that are available to you, and your right to withdraw from the study at any time.
   This information leaflet is to help you to decide if you would like to participate. You need to understand what is involved before you agree to take part in this study.
2. If you have any questions, do not hesitate to ask me.
3. You should not agree to take part unless you are satisfied about all the procedures involved.
4. You may not participate in another investigational medicine research study, nor take any other investigational medicine during your participation in this study.
5. You should not have participated in an investigational medicine research study within the past 60 days.
6. Please be open with me regarding your health history, since you may otherwise harm yourself by participating in this study.

A. Protocol …….. English Informed Consent Participant Initials: ____ ____ __
B. Version 1……. (Dated 05/08/2012)
C. Investigator's name : Dr Palesa Motshabi
D. Approved by Wits HREC
E. Date approved: …/……../……. Participant Number: _____

REF: SOP
Version:

7. If you decide to take part in this study, you will be asked to sign this document to confirm that you understand the study. You will be given a copy to keep.
8. If you have a personal doctor, please discuss with or inform him/her of your possible participation in this study. If you wish, I can also notify your personal doctor in this regard.

2. PURPOSE OF THE STUDY:

- You have been diagnosed as suffering from Coronary Artery Disease and I would like you to consider taking part in the research of a new medicine, called Dexmedetomidine.
- The purpose of this study is to determine whether the new drug, Dexmedetomidine, will improve your heart's function after surgery by protecting your heart during surgery.
- This study will compare Dexmedetomidine (Precedex) with Placebo.

3. PLACEBO

- A **placebo is an inactive substance** and it does not contain any medicine.
- You will be randomly allocated to one or other treatment (i.e. like spinning a coin). Neither you nor I will know which treatment you are receiving during your participation in the study. This procedure helps to ensure that the information gathered during the study is accurate. In case of an emergency, it will however be possible to determine which treatment you have been receiving.

4. LENGTH OF THE STUDY AND NUMBER OF PARTICIPANTS:

- The study will be performed in South Africa only.
- Approximately 90 participants will participate in this study in South Africa.
- In South Africa 90 participants will be enrolled at Charlotte Maxeke Johannesburg Academic Hospital. The participants will be between the ages of 18 and 75 years.
- The total amount of time required for your participation in this study will be a maximum of one years
- You will be asked to visit me two times during the study.

5. PROCEDURES:

- If you agree to take part in this study, you will first be asked questions and examined to see if you qualify for this study.
- Before receiving your first dose of study medication, you will be prepared for surgery in the standard way that our patients are prepared. You will be asked questions about your other medical conditions and the medication you are taking. You will be examined and have routine blood tests performed.
- Once you arrive in the operating room, the following will be done:

  Before the medication is commenced, your blood samples, blood pressure and heart rate will be recorded. Once you have been put to sleep, more measurements of your blood pressure, heart rate will be recorded. Blood samples will again be taken from you 2 hours, 18 hours and 24 hours after commencement of your operation (3 times). The total amount of blood taken from you will be 20

millilitres (+- 4 teaspoons i.e maximum of 5 tubes). Additionally, the amount of medication supporting your heart (Inotropes) will be measured. The blood samples are taken to measure the levels of your heart enzymes. The blood pressure and heart rate recordings will be used to monitor the effects of the drug on your heart function.

6. WILL ANY OF THESE STUDY PROCEDURES RESULT IN DISCOMFORT OR INCONVENIENCE?

- The drawing of your blood is normally done as part of routine medical care and presents no additional risk of discomfort as it is drawn from the drip which would be inserted as part of the normal anaesthetic you would otherwise have even if you were not taking part in the study. The total amount of blood taken from you will be 20 millilitres (+- 4 teaspoons i.e maximum of 5 tubes) over the course of the entire study.

7. RISKS OF THE STUDY MEDICINE:

In previous studies involving the same medication, some participants have reported experiencing side effects, which included:

Major drug interactions

- Dexmedetomidine administered with Propoxyphene can lead to drug related death, particularly in patients with a history of suicide tendencies, emotional disorders, alcohol and drug abuse.
- The central nervous system and respiratory effects of sodium oxybate and dexmedetomidine may potentiate each other.
- Tinazide has alpha adrenergic activity and may potentiate the hypotensive effects of dexmedetomidine.

Minor drug interactions

- Combining dexmedetomidine with fentanyl, haloperidol, midazolam, promethazine, propofol, seroquel diazepam and alcohol may lead to an increase in the central nervous system, cardiac and respiratory depressant effects.

Other Adverse Events

- The following are treatment-emergent adverse events (incidence ≤1%) from phase II/III continuous infusion ICU trials involving all Dexmetdetomidine-treated patients (N=576). Although the events reported did occur during treatment with Dexmedetomidine, **they were not necessarily caused by it.**
- Body as a whole: allergic reaction, ascites, back pain, chest pain, oedema, syncope, withdrawal syndrome.
- Cardiovascular: blood pressure fluctuation, circulatory failure, cyanosis .

- Central and peripheral nervous system disorders: dizziness, headache, neuralgia, neuritis, neuropathy, paresthesia, paralysis, paresis, speech disorder.
- Gastrointestinal: abdominal pain, diarrhoea, eruction, mucosal ulceration.
- Heart rate and rythm disorders: T wave inversion, supraventricular tachycardia, extra systoles.
- Liver and Biliary System disorders: AG ratio raised, hepatic function abnormal, increased GGT, increased SGOP, increased SGPT, jaundice.
- Metabolic and Nutritional disorders: acidosis, lactic acidosis, respiratory acidosis, diabetes mellitus, hyperglycaemia, hyperkalaemia, hypovolaemia, hypokalaemia, hypoproteinaemia, increased alkaline phosphatise, increased BUN, increased NPN.
- Musculoskeletal system disorders: muscle weakness.
- Myo-, endo-, pericardial valve disorders: angina pectoris, myocardial infarction, myocardial ischaemia.
- Platelet, bleeding and clotting disorders: coagulation disorders, disseminated intravascular coagulation, haematoma, abnormal platelets, decreased prothrombin, thrombocytopenia.
- Psychiatric disorders: Confusion, anxiety, delirium, depression, hallucination, illusion, nervousness.
- Resistance mechanism disorders: Infection, fungal infection, sepsis.

- Respiratory system: adult respiratory stress syndrome, apnoea, bronchial obstruction, bronchospasm, coughing, dyspnoea, emphysema, haemoptysis, hemothorax, hypercapnia, hypoventilation, pneumonia, pulmonary congestion, respiratory depression, sputum increased, stridor.
- Skin and appendage disorders: rash erythematous, increased sweating.
- Urinary system disorders: hematuria, renal failure acute, renal function abnormal, urinary retention.
- Vascular disorders: cerebral haemorrhage, peripheral ischaemia, vascular disorder, vasodilation.
- Vision disorders: diplopia, photopsia, abnormal vision.
- White cell disorders: leukocytosis.

7. UNFORSEEN RISKS:

- The study medicine is investigational and there may be other risks or side effects which are unforeseen or unknown. You should immediately contact me if any side effects occur throughout your participation in this study.

8. BENEFITS:

The potential benefit from your participation in this study may be control of your heart function

Dexmedetomidine (Precedex) has been shown to protect the heart in patients undergoing other operations. It is hoped that it may protect the heart in coronary artery bypass surgery as well.

- However, you may not benefit from this study.
- Your participation in this study will contribute to medical knowledge that may help other patients that, like you, have coronary artery disease.

9. ALTERNATIVE TREATMENT:

- There is no direct alternative treatment used at this stage.
- If you decide not to take part in this study you will still receive the best current care, from your usual doctor. This may or may not include the study medicine. It may also entail the anaesthetic plan that includes a volatile anaesthetic, which will not be used for the patients participating in the study. The volatile anaesthetic is a part of the normal regimen of cardiac anaesthesia used as an alternative to total intravenous anaesthesia.

ARE THERE ANY WARNINGS OR RESTRICTIONS CONCERNING MY PARTICIPATION IN THIS STUDY?

- If you are pregnant, breastfeeding or planning to become pregnant during the study period, you may not take part in the study.
- If you are a woman who can become pregnant you must use suitable contraceptive measures during the study and for 1 Month after you stop taking the study medicine, as the safety of this medicine during pregnancy has not been established. You must also read and sign the Supplementary Informed Consent for Women of Childbearing Potential (14 Years and Older).
- If you are a man who can father a child, suitable contraceptive measures should be used during the study and for 1 month after you stop taking the study medicine.

INTERACTIONS:

- It is important that you let me know of any medicines (both prescriptions and over-the-counter medicines), alcohol or other substances that you are currently taking.
- During this study, you should not take the drugs mentioned below on your own without supervision as they have serious interactions:

Major drug interactions

- Dexmedetomidine administered with Propoxyphene can lead to drug related death, particularly in patients with a history of suicide tendencies, emotional disorders, alcohol and drug abuse.

- The central nervous system and respiratory effects of sodium oxybate and dexmedetomidine may potentiate each other.
- Tinazide has alpha adrenergic activity and may potentiate the hypotensive effects of dexmedetomidine.

Minor drug interactions

- Combining dexmedetomidine with fentanyl, haloperidol, midazolam, promethazine, propofol, seroquel, diazepam and alcohol may lead to an increase in the central nervous system, cardiac and respiratory depressant effects.
- If you have to, please inform me **immediately**.

10. **RIGHTS AS A PARTICIPANT IN THIS STUDY (VOLUNTARY)**

Your participation in this study is entirely voluntary and you can decline to participate, or stop at any time, without stating any reason. Your withdrawal will not affect your access to other medical care.

- Discontinuation of study treatment:

You must inform me if you wish to stop taking your study medicine.

I will supervise any discontinuation with your health as first priority.

11. NEW FINDINGS:

A. Protocol …….. English Informed Consent Participant Initials: ____ ____ __
B. Version 1……. (Dated 05/08/2012)
C. Investigator's name : Dr Palesa Motshabi
D. Approved by Wits HREC
E. Date approved: …/……../……. Participant Number: _____

REF: SOP
Version:

- I will provide you with any additional information that becomes available during the study, which may affect your willingness to continue on the study.

12. **WITHDRAWAL:**

Your withdrawal will not affect your access to other medical care.

- I retain the right to withdraw you from the study if it is considered to be in your best interest. If your participation is ended early, you may be asked to return for study-ending tests and procedures for your safety
- If you did not give an accurate history or did not follow the guidelines of the study and the regulations of the study facility, you may be withdrawn from the study at any time.
- ***Pregnancy:*** Because the safety during pregnancy of the medicine used in this study has not been established, you will be immediately withdrawn from the study, if you become pregnant during your participation in the study. All aspects of healthcare related to your pregnancy and infant will be your responsibility. We will require access to your medical records and those of your child, from the time you became pregnant and for a minimum of 6 weeks after the baby is born.

13. EMERGENCY CARE AND HOSPITALISATION:

- If you seek emergency care or if hospitalisation is required at any time during the study up to 12 month/s after taking the last dose of study medicine, please tell the treating doctor **that you have enrolled in this research study** and that **I must be informed.**

A. Protocol …….. English Informed Consent Participant Initials: ____ ____ __
B. Version 1……. (Dated 05/08/2012)
C. Investigator's name : Dr Palesa Motshabi
D. Approved by Wits HREC
E. Date approved: …/……../……. Participant Number: _____

REF: SOP
Version:

14. FINANCIAL ARRANGEMENTS:

- *THE STUDY DOCTOR* will provide payment for all study procedures and reasonable medical expenses that you may incur as a direct result of this study as determined by her.
- Neither you nor your medical scheme will be expected to pay for any study medication, study related visit or study procedures.
- ***THE COSTS OF ALL STUDY-RELATED PROCEDURES WOULD BE PAID BY THE STUDY DOCTOR.***

15. REIMBURSEMENT FOR STUDY PARTICIPATION:

- You will not be paid to participate in this study but your **transport and, when necessary, refreshment costs will be reimbursed adequately**, according to MCC requirements.

16. INSURANCE:

THE STUDY DOCTOR has obtained insurance for you and herself in the event of study related injury or illness. A study-related injury or illness is one that occurs as a direct result of the administration of the study medicine or of study-specific procedures.

A. Protocol …….. English Informed Consent Participant Initials: ____ ____ __
B. Version 1……. (Dated 05/08/2012)
C. Investigator's name : Dr Palesa Motshabi
D. Approved by Wits HREC
E. Date approved: …/……../……. Participant Number: _____

REF: SOP
Version:

17. ABPI STATEMENT ON COMPENSATION:

The insurance will provide compensation for reasonable medical expenses incurred as a result of study-related injury or illness, determined according to the guidelines laid down by the **Association of the British Pharmaceutical Industry (ABPI Guidelines),** and **Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa.**

- You must notify me immediately of any complications, side effects and/or injuries during the study and the nature of the expenses to be covered.
- If a research related injury occurs, you have not waived any of the legal rights which you otherwise would have as a participant in this study by signing this form.

Further detailed information on the payment of medical treatment and compensation due to injury can be obtained from me. I have a copy of the ABPI Guidelines and the Insurance Certificate, should you wish to review them.

The insurance does not cover and will not pay for:

- Medical treatment of ***other*** injuries or illnesses
- Injury caused by non-observance of the protocol

A. Protocol …….. English Informed Consent Participant Initials: ____ ____ __
B. Version 1……. (Dated 05/08/2012)
C. Investigator's name : Dr Palesa Motshabi
D. Approved by Wits HREC
E. Date approved: …/……../……. Participant Number: _____

REF: SOP
Version:

I am indemnified by the INSURANCE conditional upon:

- My compliance with the applicable requirements of the study protocol
- My compliance with the regulations of the Medicines Control Council and the University of the Witwatersrand, Human Research Ethics Committee (HREC).
- The handling and administration of the study medication in accordance with instructions and guidelines provided in the protocol, subsequent amendments and related documents
- The indemnification is not intended to be and is not a substitute for my personal malpractice insurance.

Please note that if you have a life insurance policy you should enquire whether your insurance company requires notification of your intention to participate in a clinical study. Information to date is that it should not affect any life insurance policy taken out. Nevertheless, you are strongly advised to clarify it with the company concerned.

18. ETHICAL APPROVAL:

- This clinical study protocol has been submitted to the University of the Witwatersrand, **Human Research Ethics Committee (HREC)** and written approval has been granted by that committee.

A. Protocol …….. English Informed Consent Participant Initials: ____ ____ __
B. Version 1……. (Dated 05/08/2012)
C. Investigator's name : Dr Palesa Motshabi
D. Approved by Wits HREC
E. Date approved: …/……../……. Participant Number: _____

REF: SOP
Version:

- The study has been structured in accordance with the **Declaration of Helsinki** (last updated: October 2008), which deals with the recommendations guiding doctors in biomedical research involving human participants. A copy may be obtained from me should you wish to review it.
- This study is sponsored by the university administered research funds.

  I do not have any financial or personal interests with this organisation that may bias my actions.

19. SOURCE OF ADDITIONAL INFORMATION:

For the duration of the study, you will be under the care of Dr Motshabi. If at any time between your visits, you feel that any of your symptoms are causing you any problems, or you have any questions during the study, please do not hesitate to contact me.

Other doctors from this department who are assisting with recruitment of patients are:

- *DR PALESA MOGANE CELL: 0731731440*
- *DR ELLEN KEMP CELL : 0835459034*
- *DR KGOPOTSO MONONYANE CELL: 0837742408*
- *DR THENJIWE HLONGWANE CELL : 0846843654*

The 24-hour telephone number through which you can reach me or another authorised person, is 0834321994.

A. Protocol …….. English Informed Consent Participant Initials: ____ ____ __
B. Version 1……. (Dated 05/08/2012)
C. Investigator's name : Dr Palesa Motshabi
D. Approved by Wits HREC
E. Date approved: …/……../……. Participant Number: _____

REF: SOP
Version:

- If you want any information regarding your **rights as a research participant, or complaints regarding this research study**, you may contact Prof. Cleaton-Jones, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee established to help protect the rights of research participants at (011) 717 2301.
- For **research information** you can contact Dr Motshabi at 0834321994

20. MEDICINES CONTROL COUNCIL SOUTH AFRICA - MCC

If you have questions about this trial you should first discuss them with your doctor or the ethics committee (contact details as provided on this form). After you have consulted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the Medicines Control Council (MCC) South Africa at:

The Registrar

Medicines Control Council SA

Department of Health

Private Bag X828

PRETORIA

A. Protocol …….. English Informed Consent Participant Initials: ____ ____ __
B. Version 1……. (Dated 05/08/2012)
C. Investigator's name : Dr Palesa Motshabi
D. Approved by Wits HREC
E. Date approved: …/……../……. Participant Number: _____

REF: SOP
Version:

0001

Fax: (012) 395 9201

E-mail: helam@health.gov.za and mogobm@health.gov.za

21. CONFIDENTIALITY:

- All information obtained during the course of this study, including hospital records, personal data and research data will be kept strictly confidential. Data that may be reported in scientific journals will not include any information that identifies you as a participant in this study.
- Authorised person in the form of a safety monitoring team may inspect records during the course of the study.
- This information will be reviewed by authorised representatives of the research team and monitoring team.
- The information might also be inspected by the University of the Witwatersrand, Human Research Ethics Committee (HREC), the South African Medicines Control Council (MCC) and/or the United States Food and Medicine Administration (FDA), as well as your personal doctor. Therefore, you hereby authorise

me to release your medical records to the South African Medicines Control Council and the University of the Witwatersrand, Human Research Ethics Committee (HREC).

- These records will be utilised by them only in connection with carrying out their obligations relating to this clinical study.
- Any information uncovered regarding your test results or state of health as a result of your participation in this study will be held in strict confidence. You will be informed of any finding of importance to your health or continued participation in this study but this information will not be disclosed to any third party in addition to the ones mentioned above without your written permission. The only exception to this rule will be cases of communicable diseases where a legal duty of notification of the Department of Health exists. In this case, you will be informed of my intent to disclose such information to the authorised state agency.

22. PERSONAL DOCTOR / SPECIALIST NOTIFICATION OPTION:

Please indicate below, whether you want me to notify your personal doctor or your specialist of your participation in this study:

- **YES**, I want you to inform my personal doctor / specialist of my participation in this study.
- **NO**, I do not want you to inform my personal doctor / specialist of my participation in this study.
- **I do not have** a personal doctor / specialist

23. PARTICIPANT QUESTIONS *?:*

Did the participant raise any questions?

YES / NO

If YES – What where they:

A. Protocol …….. English Informed Consent
B. Version 1……. (Dated 05/08/2012)
C. Investigator's name : Dr Palesa Motshabi
D. Approved by Wits HREC
E. Date approved: …/……../…….

Participant Initials: ____ ____ __

Participant Number: _____

REF: SOP
Version:

INFORMED CONSENT:

- I hereby confirm that I have been informed by the study doctor, Dr Palesa Motshabi, about the nature, conduct, benefits and risks of clinical study: **DEXMEDETOMIDINE DURING CORONARY ARTERY BYPASS GRAFT SURGERY: EFFECTS ON MYOCARDIAL ISCHAEMIC AND INFLAMMATORY MARKERS, MORTALITY AND LENGTH OF INTENSIVE CARE UNIT AND HOSPITAL STAY**
- I have also received, read and understood the above written information (Participant Information Leaflet and Informed Consent) regarding the clinical study.
- I am aware that the results of the study, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a study report.
- In view of the requirements of research, I agree that the data collected during this study can be processed in a computerised system by Dr Motshabi or on her behalf.
- I may, at any stage, without prejudice, withdraw my consent and participation in the study.
- I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the study.

PARTICIPANT:

A. Protocol …….. English Informed Consent
B. Version 1……. (Dated 05/08/2012)
C. Investigator's name : Dr Palesa Motshabi
D. Approved by Wits HREC
E. Date approved: …/……../…….

Participant Initials: ____ ____ __

Participant Number: _____

REF: SOP
Version:

Printed Name Signature / Mark or Thumbprint Date and Time

I, Dr....., herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

STUDY DOCTOR:

Printed Name **Signature** **Date and Time**

TRANSLATOR / OTHER PERSON EXPLAINING INFORMED CONSENT…….....(DESIGNATION):

Printed Name **Signature** **Date and Time**

WITNESS (If applicable):

Printed Name Signature Date and Time

A. Protocol …….. English Informed Consent Participant Initials: ____ ____ __
B. Version 1……. (Dated 05/08/2012)
C. Investigator's name : Dr Palesa Motshabi
D. Approved by Wits HREC
E. Date approved: …/……../……. Participant Number: _____

REF: SOP
Version:

VERBAL PARTICIPANT INFORMED CONSENT:

(Applicable when participants cannot read or write or are incapable of giving consent)

- I, the undersigned, Dr.....have read and have explained fully to the participant, named ..... and/or his/her relative/ friend/legal representative, ..., the participant information leaflet.
- The account I have given has explained both the possible risks and benefits of the study as well as the alternative treatments available for his/her illness. The participant and/or his/ her relative/friend/legal representative understands these.
- The participant and/or his/her relative/friend/legal representative indicated that he/she understands that the participant will be free to withdraw from the study at any time for any reason and without jeopardising his/her subsequent treatment.
- I have also informed the participant and/or his/her relative/friend/legal representative of the existence of relevant compensation arrangements in case of an injury attributable to the medicine(s) used in the clinical study, to which he/she agrees.

A. Protocol …….. English Informed Consent Participant Initials: ____ ____ __
B. Version 1……. (Dated 05/08/2012)
C. Investigator's name : Dr Palesa Motshabi
D. Approved by Wits HREC
E. Date approved: …/……../……. Participant Number: _____

REF: SOP
Version:

I hereby certify that, the participant and/or his/her relative/friend/legal representative, acting on his/her behalf, has agreed to participate in this study.

PARTICIPANT:

Printed Name **Mark or Thumbprint (if applicable)** **Date and Time**

STUDY DOCTOR:

Printed Name **Signature** **Date and Time**

TRANSLATOR / OTHER PERSON EXPLAINING INFORMED CONSENT:

……..…**(DESIGNATION)**

A. Protocol …….. English Informed Consent
B. Version 1……. (Dated 05/08/2012)
C. Investigator's name : Dr Palesa Motshabi
D. Approved by Wits HREC
E. Date approved: …/……../…….

Participant Initials: ____ ____ __

Participant Number: _____

REF: SOP
Version:

,UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Palesa Motshabi

CLEARANCE CERTIFICATE	M111179
PROJECT	D Dexmedetomidine during Coronary Artery Bypass Graft Surgery: Effects on Ischaemic and Inflammatory Markers, Mortality, Length Intensive Care Unit and Hospital Stay
INVESTIGATORS	Dr Palesa Motshabi
DEPARTMENT	Department of Anaesthesia
DATE CONSIDERED	25/11/2011
DECISION OF THE COMMITTEE*	Approed unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 11/09/2013 **CHAIRPERSON** .....
(Professor P E Cleaton Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr M Nethononda

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 6: Trial Insurance

STALKER
HUTCHISON
ADMIRAL

"NO-FAULT" COMPENSATION FOR CLINICAL TRIALS
INSURANCE CERTIFICATE

POLICY NUMBER:	P00369
BROKER:	Highgrove Financial Services (Pty) Ltd (VAT no. 4210171783)
INSURED:	Dr P. Motshabi
TRIAL:	Dexmedetomidine during coronary artery bypass graft surgery: Effects on myocardial ischaemic and inflammatory markers, mortality and length of intensive care unit and hospital stay.
TYPE OF TESTING:	Phase 1, 2 and 3
NUMBER OF RESEARCH SUBJECTS:	90
PERIOD OF INSURANCE:	12 Months from Inception of the Trial
RETROACTIVE DATE:	Inception
LIMIT OF INDEMNITY (EXCLUDING VAT):	R 10,000,000 in the annual aggregate
DEDUCTIBLE (EXCLUDING VAT):	R 25,000 each and every claim
PREMIUM (INCLUDING VAT):	R 45,000.00
POLICY WORDING:	"No-Fault" Compensation for Clinical Trials as per the Master Policy
EXTENSION:	Extended Reporting Period – Additional Period of 36 Months
ADDITIONAL CONDITIONS:	Exclusion No 7.22 is amended to read as follows: "arising out of the use of Research Subjects who may be considered to be children and for whom consent has not been provided pursuant to the applicable provisions of the Children's Act No. 28 of 2005 (as amended from time to time) or any succeeding legislation."

SHA is a wholly owned subsidiary of Santam Limited. Santam is a level 3 BBBEE company, and has been awarded a triple A claims paying ability rating by GCR.
The Pavilion, The Wanderers Office Park, 52 Corlett Drive, Illovo, 2196. PO Box 55347, Northlands, 2116, Johannesburg, South Africa.
Tel: +27 11 731 3600 Fax: +27 11 447 0080 (Exec) +27 11 447 0081/2(UW) +27 11 447 0083 (Claims) +27 11 447 0084 (Accts)
Stalker Hutchison Admiral (Pty) Limited Reg. No. 1985/000368/07 Vat No. 4310103082
Authorised Financial Services Provider (licence number 2167)
Directors: I M Kirk (Chairman), B B Palmer (CEO), H J Horne, Q M Matthew, J Melville, M J Reyneke
A member of SAUMA

Appendix 7: Consort Checklist

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	VI
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	VI/9
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	2
	2b	Specific objectives or hypotheses	8
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	50
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	51
	4b	Settings and locations where the data were collected	51
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	51– 56
Outcomes	6a	Completely defined pre– specified primary and secondary outcome measures, including how and when they were assessed	57
	6b	Any changes to trial outcomes after the trial commenced, with reasons	60
Sample size	7a	How sample size was determined	80
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	50
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	50
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	50
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	50

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	50
	11b	If relevant, description of the similarity of interventions	53
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	56
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	56, 87, 93, 106, 122
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	60
	13b	For each group, losses and exclusions after randomisation, together with reasons	60
Recruitment	14a	Dates defining the periods of recruitment and follow– up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	62
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	62
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	62,63,64
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre– specified from exploratory	82,89,102 ,118,123
Harms	19	All– important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	81,88,101 ,117 ,125
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	125
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	125
Other information			
Registration	23	Registration number and name of trial registry	

Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	VIII

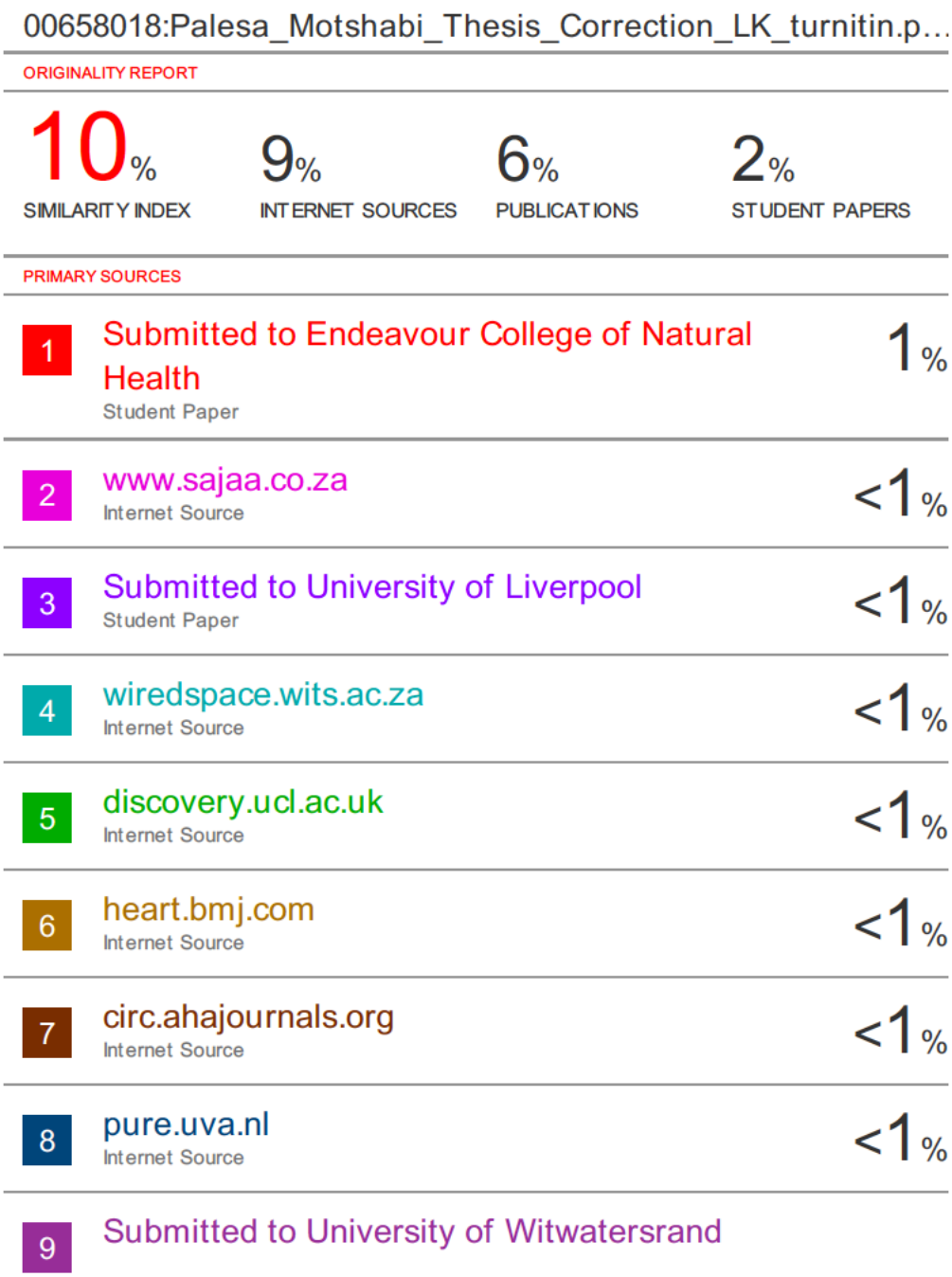
Consort 2010 (304). This table is copied in terms of Section 12 (Fair Dealing) of the SA Copyright Act No. 98 of 1978 (as amended).

Appendix 8: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE Does dexmedetomidine reduce mortality in cardiac surgery? A systematic review and meta-analysis of randomised controlled trials			128
Title	1	Identify the report as a systematic review, meta-analysis, or both.	128
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	130
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	131/132
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	131
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	131
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	131
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	133
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	133
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	133
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	134
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	139

Summary measures	13	State the principal summary measures (e.g. risk ratio, difference in means).	136
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g. I^2) for each meta-analysis.	136

Appendix 9: Turnitin Report



00658018:Palesa_Motshabi_Thesis_Correction_LK_turnitin.p...

ORIGINALITY REPORT

10%	9%	6%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Submitted to Endeavour College of Natural Health Student Paper	1%
2	www.sajaa.co.za Internet Source	<1%
3	Submitted to University of Liverpool Student Paper	<1%
4	wiredspace.wits.ac.za Internet Source	<1%
5	discovery.ucl.ac.uk Internet Source	<1%
6	heart.bmj.com Internet Source	<1%
7	circ.ahajournals.org Internet Source	<1%
8	pure.uva.nl Internet Source	<1%
9	Submitted to University of Witwatersrand	

	Student Paper	<1%
10	ccforum.biomedcentral.com Internet Source	<1%
11	www.esahq.org Internet Source	<1%
12	www.science.gov Internet Source	<1%
13	clinchem.aaccjnls.org Internet Source	<1%
14	icaa.ir Internet Source	<1%
15	Bronze-da-Rocha, Elsa. "MicroRNAs expression profiles in cardiovascular diseases. (Report)", BioMed Research International, Annual 2014 Issue Publication	<1%
16	dspace.nwu.ac.za Internet Source	<1%
17	www.wits.ac.za Internet Source	<1%
18	bmcpublichealth.biomedcentral.com Internet Source	<1%
19	Submitted to University of Wales Institute,	

	Cardiff Student Paper	<1%
20	journals.plos.org Internet Source	<1%
21	Submitted to Coventry University Student Paper	<1%
22	Submitted to Universiteit van Amsterdam Student Paper	<1%
23	scholar.sun.ac.za Internet Source	<1%
24	www.nice.org.uk Internet Source	<1%
25	jtcs.ctsnetjournals.org Internet Source	<1%
26	link.springer.com Internet Source	<1%
27	issuu.com Internet Source	<1%
28	open.uct.ac.za Internet Source	<1%
29	Schoenenberger, A. W., F. Stallone, B. Walz, M. Bergner, R. Twerenbold, T. Reichlin, B. Zogg, C. Jaeger, P. Erne, and C. Mueller. "Incremental value of heart-type fatty acid-binding protein in	<1%

	suspected acute myocardial infarction early after symptom onset", European Heart Journal Acute Cardiovascular Care, 2015. Publication	
30	www.sbccv.org.br Internet Source	<1%
31	tel.archives-ouvertes.fr Internet Source	<1%
32	homepage.psy.utexas.edu Internet Source	<1%
33	njl-admin.nihr.ac.uk Internet Source	<1%
34	B. M. Biccard. "Dexmedetomidine and cardiac protection for non-cardiac surgery: a meta-analysis of randomised controlled trials", Anaesthesia, 01/2008 Publication	<1%
35	Submitted to Kenyatta University Student Paper	<1%
36	www.scribd.com Internet Source	<1%
37	www.doria.fi Internet Source	<1%
38	Motshabi, P. "Myocardial ischaemia during coronary artery bypass graft surgery: a review	<1%

	of intervention strategies (Part 2)", Southern African Journal of Anaesthesia and Analgesia, 2012. Publication	
39	herkules.oulu.fi Internet Source	<1%
40	www.thecochranelibrary.com Internet Source	<1%
41	Joseph D. Tobias. "Dexmedetomidine: Applications in pediatric critical care and pediatric anesthesiology", Pediatric Critical Care Medicine, 03/2007 Publication	<1%
42	ejcts.ctsnetjournals.org Internet Source	<1%
43	theses.gla.ac.uk Internet Source	<1%
44	Carless, Paul A, Fraser D Rubens, Danielle M Anthony, Dianne O'Connell, David A Henry, and Paul A Carless. "Platelet-rich-plasmapheresis for minimising peri-operative allogeneic blood transfusion", Cochrane Database of Systematic Reviews, 2003. Publication	<1%
45	Suzi Robertson-Malt. "Prophylactic steroids for pediatric open heart surgery", Cochrane	<1%

	Database of Systematic Reviews Reviews, 10/17/2007 Publication	
46	www.csahq.org Internet Source	<1%
47	www.cvja.co.za Internet Source	<1%
48	academic.oup.com Internet Source	<1%
49	qjmed.oxfordjournals.org Internet Source	<1%
50	www.wyeth.ca Internet Source	<1%
51	www.unicef.org Internet Source	<1%
52	www.dovepress.com Internet Source	<1%
53	www.biomed.cas.cz Internet Source	<1%
54	digital.library.adelaide.edu.au Internet Source	<1%
55	www.healthcare-today.co.uk Internet Source	<1%
	ats.ctsnetjournals.org	

56	Internet Source	<1%
57	sign.ac.uk Internet Source	<1%
58	content.onlinejacc.org Internet Source	<1%
59	onlinelibrary.wiley.com Internet Source	<1%
60	pdfs.semanticscholar.org Internet Source	<1%
61	unitec.researchbank.ac.nz Internet Source	<1%
62	www.jove.com Internet Source	<1%
63	tampub.uta.fi Internet Source	<1%
64	"Total Intravenous Anesthesia and Target Controlled Infusions", Springer Nature, 2017 Publication	<1%
65	bmcanesthesiol.biomedcentral.com Internet Source	<1%
66	lrd.yahooapis.com Internet Source	<1%
	www.meja.aub.edu.lb	

67	Internet Source	<1%
68	Kim, Hyo-Jin, Won Ho Kim, Gahyun Kim, Eunhee Kim, Mi-Hye Park, Byung Seop Shin, Woo Seog Sim, Chung Su Kim, Young Tak Lee, and Hyun Sung Cho. "A comparison among infusion of lidocaine and dexmedetomidine alone and in combination in subjects undergoing coronary artery bypass graft: A randomized trial", Contemporary Clinical Trials, 2014. Publication	<1%
69	smw.ch Internet Source	<1%
70	www.socru.org Internet Source	<1%
71	www.obesityresearch.org Internet Source	<1%
72	www.austin.org.au Internet Source	<1%
73	Submitted to North West University Student Paper	<1%
74	Coronary Graft Failure, 2016. Publication	<1%
75	www.trialsjournal.com	

	Internet Source	<1%
76	Xiaohui Chi, Mingfeng Liao, Xin Chen, Yilin Zhao, Liu Yang, Ailin Luo, Hui Yang. "Dexmedetomidine Attenuates Myocardial Injury in Off-Pump Coronary Artery Bypass Graft Surgery", Journal of Cardiothoracic and Vascular Anesthesia, 2016 Publication	<1%
77	www.sign.ac.uk Internet Source	<1%
78	jcdr.net Internet Source	<1%
79	documents.mx Internet Source	<1%
80	www.anesthesia-analgesia.org Internet Source	<1%
81	www.slideshare.net Internet Source	<1%
82	www.ncbi.nlm.nih.gov Internet Source	<1%
83	elbahey.com Internet Source	<1%
84	repositorio.ufsm.br Internet Source	<1%

85	www.plosone.org Internet Source	<1%
86	www.co.middlesex.nj.us Internet Source	<1%
87	ompetencias Internet Source	<1%
88	dl4a.org Internet Source	<1%
89	Study Investigators. "Improved myocardial protection during coronary artery surgery with glucose-insulin-potassium: A randomized controlled trial", The Journal of Thoracic and Cardiovascular Surgery, 200601 Publication	<1%
90	scholarcommons.usf.edu Internet Source	<1%
91	epublications.uef.fi Internet Source	<1%
92	S. Suttner. "Association of N-terminal pro-brain natriuretic peptide and cardiac troponin T with in-hospital cardiac events in elderly patients undergoing coronary artery surgery", European Journal of Anaesthesiology, 10/2008 Publication	<1%
	collections.plymouth.ac.uk	

93	Internet Source	<1%
94	spotidoc.com Internet Source	<1%
95	www.ajol.info Internet Source	<1%
96	ccforum.com Internet Source	<1%
97	Giorgio Sirugo. "Genetic studies of African populations: an overview on disease susceptibility and response to vaccines and therapeutics", Human Genetics, 07/2008 Publication	<1%
98	www.termedia.pl Internet Source	<1%
99	eurheartj.oxfordjournals.org Internet Source	<1%
100	www.himki.ru Internet Source	<1%
101	www.sasaweb.com Internet Source	<1%
102	www.clinicalconsensusreports.com Internet Source	<1%
103	Coronary Microvascular Dysfunction, 2014.	

	Publication	<1%
104	Submitted to CSU, Long Beach Student Paper	<1%
105	Submitted to University of Derby Student Paper	<1%
106	repub.eur.nl Internet Source	<1%
107	Guenancia, Charles Pujos, Charline Debom. "Incidence and predictors of new-onset silent atrial fibrillation after coronary artery bypass graft ", BioMed Research International, Annual 2015 Issue Publication	<1%
108	Submitted to University of Ulster Student Paper	<1%
109	Submitted to Maryville University Student Paper	<1%
110	Submitted to University of Aberdeen Student Paper	<1%
111	www.ishib.org Internet Source	<1%
112	Submitted to Cardiff University Student Paper	<1%

113	Giovanni Landoni, Vladimir Lomivorotov, Simona Silvetti, Caetano Nigro Neto et al. "Nonsurgical Strategies to Reduce Mortality in Patients Undergoing Cardiac Surgery: An Updated Consensus Process", Journal of Cardiothoracic and Vascular Anesthesia, 2018 Publication	<1%
114	Submitted to Laureate Higher Education Group Student Paper	<1%
115	Jresat , Nesreen Fraih. "Economic Impacts of Applying Electronic Cheque Clearing Solution a Case : Study - State of Qatar (2001 - 2005)", Economic Impacts of Applying Electronic Cheque Clearing Solution a Case : Study - State of Qatar (2001 - 2005) Publication	<1%
116	Submitted to University of South Florida Student Paper	<1%
117	Serruys, Patrick W., Marie-Claude Morice, A. Pieter Kappetein, Antonio Colombo, David R. Holmes, Michael J. Mack, Elisabeth Ståhle, Ted E. Feldman, Marcel van den Brand, Eric J. Bass, Nic Van Dyck, Katrin Leadley, Keith D. Dawkins, and Friedrich W. Mohr. "Percutaneous Coronary Intervention versus Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease", New England Journal of Medicine,	<1%

	2009. Publication	
118	www.inpim.org Internet Source	<1%
119	Waller, Benjamin Ogonowska-Slodownik, Anna Vitor, Manuel Lambeck, Johan Daly, Daniel Kujala, Urho M.. "Effect of therapeutic aquatic exercise on symptoms and function associated with lower limb osteoarth", Physical Therapy, Oct 2014 Issue Publication	<1%
120	circheartfailure.ahajournals.org Internet Source	<1%
121	medicine.yale.edu Internet Source	<1%
122	www.intechopen.com Internet Source	<1%
123	www.biomedcentral.com Internet Source	<1%
124	lib.ugent.be Internet Source	<1%
125	www.health.gov.fj Internet Source	<1%
126	www.bioline.org.br Internet Source	<1%

127	stroke.ahajournals.org Internet Source	<1%
128	www.cancaresociety.com Internet Source	<1%
129	www.e-ceth.org Internet Source	<1%
130	physiology.usouthal.edu Internet Source	<1%
131	Submitted to Bolton Institute of Higher Education Student Paper	<1%
132	aura.abdn.ac.uk Internet Source	<1%
133	www.diva-portal.org Internet Source	<1%
134	ediss.sub.uni-hamburg.de Internet Source	<1%
135	spandidos-publications.com Internet Source	<1%
136	intl-content.nejm.org Internet Source	<1%
137	www.msac.gov.au Internet Source	<1%
	www.medlit.ru	

138	Internet Source	<1%
139	Tosun, Zeynep, Mehmet Baktir, Husnu Cemal Kahraman, Gulden Baskol, Gulen Guler, and Adem Boyaci. "Does Dexmedetomidine Provide Cardioprotection in Coronary Artery Bypass Grafting With Cardiopulmonary Bypass? A Pilot Study", Journal of Cardiothoracic and Vascular Anesthesia, 2013. Publication	<1%
140	www.hma.eu Internet Source	<1%
141	Cho, Jin Sun, Jae-Kwang Shim, Sara Soh, Min Kyung Kim, and Young-Lan Kwak. "Perioperative dexmedetomidine reduces the incidence and severity of acute kidney injury following valvular heart surgery", Kidney International, 2015. Publication	<1%
142	Mittnacht, Alexander J.C., Menachem Weiner, Martin J. London, and Joel A. Kaplan. "Anesthesia for Myocardial Revascularization", Kaplan s Cardiac Anesthesia The Echo Era, 2011. Publication	<1%
143	vts.uni-ulm.de Internet Source	<1%

144	www.ncepod.org.uk Internet Source	<1%
145	www.journals.ac.za Internet Source	<1%
146	www.frycomm.com Internet Source	<1%
147	www.phidias.us Internet Source	<1%
148	www.canberra.edu.au Internet Source	<1%
149	etheses.bham.ac.uk Internet Source	<1%
150	www.spandidos-publications.com Internet Source	<1%
151	www.medandlife.ro Internet Source	<1%
152	icvts.ctsnetjournals.org Internet Source	<1%
153	www.redorbit.com Internet Source	<1%
154	www.medicographia.com Internet Source	<1%
155	intl-ats.ctsnetjournals.org	

	Internet Source	<1%
156	www.spc.pt Internet Source	<1%
157	Masson, S., N. Agabiti, T. Vago, M. Miceli, F. Mayer, T. Letizia, U. Wienhues-Thelen, G. F. Mureddu, M. Davoli, A. Boccanelli, and R. Latini. "The fibroblast growth factor-23 and Vitamin D emerge as nontraditional risk factors and may affect cardiovascular risk", Journal of Internal Medicine, 2014. Publication	<1%
158	iai.asm.org Internet Source	<1%
159	www.nature.com Internet Source	<1%
160	coronaryarterybypassgraft.org Internet Source	<1%
161	www.cambridge.org Internet Source	<1%
162	react-profile.org Internet Source	<1%
163	ethesis.helsinki.fi Internet Source	<1%

164	www.sdsjournal.org Internet Source	<1%
165	www.snacc.org Internet Source	<1%
166	www.granorobenessere.it Internet Source	<1%
167	www.narcose.nl Internet Source	<1%
168	www.jci.org Internet Source	<1%
169	www.oncotarget.com Internet Source	<1%
170	www.thieme-connect.com Internet Source	<1%
171	www.delmarhealthcare.com Internet Source	<1%
172	jaha.ahajournals.org Internet Source	<1%
173	asianannals.ctsnetjournals.org Internet Source	<1%
174	dns2.asia.edu.tw Internet Source	<1%
175	"Critical Care Sedation", Springer Nature, 2018 Publication	

		<1%
176	jeccr.biomedcentral.com Internet Source	<1%
177	sorcan.ca Internet Source	<1%
178	Submitted to University College London Student Paper	<1%
179	anesthesia.thewithin.kr Internet Source	<1%
180	"Researchers from Sun Yat Sen University Report Details of New Studies and Findings in the Area of CI", Heart Disease Weekly, Jan 25 2015 Issue Publication	<1%
181	www.esciencecentral.org Internet Source	<1%
182	journals.sagepub.com Internet Source	<1%
183	research-information.bristol.ac.uk Internet Source	<1%
184	www.omicsonline.org Internet Source	<1%
185	www.bmj.com	

	Internet Source	<1%
186	dhsprogram.com Internet Source	<1%
187	www.mrc.ac.za Internet Source	<1%
188	www.iars.org Internet Source	<1%
189	dspace.stir.ac.uk Internet Source	<1%
190	www.davidhanauer.com Internet Source	<1%
191	journals.sbmu.ac.ir Internet Source	<1%
192	portal.research.lu.se Internet Source	<1%
193	www.medsci.org Internet Source	<1%
194	Soro, Marina, LucÃa Gallego, Vanessa Silva, MarÃa T. Ballester, Julio LlorÃ©ns, Ana AlvariÃ±o, MarÃa L. GarcÃa-Perez, Ernesto Pastor, Gerardo Aguilar, Francisco J. MartÃ, Arturo Carratala, and F. Javier Belda. "Cardioprotective effect of sevoflurane and	<1%

	propofol during anaesthesia and the postoperative period in coronary bypass graft surgery : a double-blind randomised study", European Journal of Anaesthesiology, 2012. Publication	
195	ueaeprints.uea.ac.uk Internet Source	<1%
196	bja.oxfordjournals.org Internet Source	<1%
197	www.ijcem.com Internet Source	<1%
198	www.scitechnol.com Internet Source	<1%
199	medsafe.govt.nz Internet Source	<1%
200	rc.rcjournal.com Internet Source	<1%
201	Reducing Mortality in the Perioperative Period, 2014. Publication	<1%
202	www.ics.ac.uk Internet Source	<1%
203	docplayer.net Internet Source	<1%

204	"Myocardial Ischemia and Infarction", Journal of the American College of Cardiology, 2008. Publication	<1%
205	www.anakarder.com Internet Source	<1%
206	hypertensionaha.smart01.highwire.org Internet Source	<1%
207	edoc.unibas.ch Internet Source	<1%
208	tsukuba.repo.nii.ac.jp Internet Source	<1%
209	Sivanna, Umesh Joshi, Shreedhar Babu, Balaji Jagadeesh, A.. "A comparative study of pharmacological myocardial protection between sevoflurane and desflurane at a", Indian Journal of Anaesthesia, May 2015 Issue Publication	<1%
210	ecmj.org.cn Internet Source	<1%
211	Yang Liu, Bo Sheng, Suozhu Wang, Feiping Lu, Jie Zhen, Wei Chen. "Dexmedetomidine prevents acute kidney injury after adult cardiac surgery: a meta-analysis of randomized controlled trials", BMC Anesthesiology, 2018 Publication	<1%

212	www.ortopaedi.dk Internet Source	<1%
213	www.hhr.be Internet Source	<1%
214	"Oral Session Abstracts.(Abstracts)(Report) (Author abstract)", Indian Journal of Pharmacology, Dec 2015 Issue Publication	<1%
215	panafrican-med-journal.com Internet Source	<1%
216	www.erj.ersjournals.com Internet Source	<1%
217	medlib.mef.hr Internet Source	<1%
218	Morrow, David A. Ridker, Paul M.. "C-reactive protein: Evaluating a new marker for cardiovascular disease.", Internal Medicine, Feb 2000 Issue Publication	<1%
219	blood.gov.au Internet Source	<1%
220	cdn.intechopen.com Internet Source	<1%
221	www.grg-bs.it Internet Source	<1%

222	openaccess.leidenuniv.nl Internet Source	<1%
223	preview-ccforum.biomedcentral.com Internet Source	<1%
224	www.hippokratia.gr Internet Source	<1%
225	intl.clinchem.org Internet Source	<1%
226	eprints.whiterose.ac.uk Internet Source	<1%
227	era.library.ualberta.ca Internet Source	<1%
228	www.fisme.science.uu.nl Internet Source	<1%
229	extras.springer.com Internet Source	<1%
230	Pan, Wanying, Yueting Wang, Lin Lin, Ge Zhou, Xiaoxiao Hua, and Liqiu Mo. "Outcomes of dexmedetomidine treatment in pediatric patients undergoing congenital heart disease surgery: a meta-analysis", Pediatric Anesthesia, 2015. Publication	<1%
231	Antonio Salsano, Daniele Roberto Giacobbe,	

	Elena Sportelli, Guido Maria Olivieri et al. "Aortic cross-clamp time and cardiopulmonary bypass time: prognostic implications in patients operated on for infective endocarditis", Interactive CardioVascular and Thoracic Surgery, 2018 Publication	<1%
232	G D Angelini. "Inflammatory response and cardioprotection during open-heart surgery: the importance of anaesthetics", British Journal of Pharmacology, 01/2008 Publication	<1%
233	Savell, Emily Gilmore, Anna B. Sims, Mic. "The environmental profile of a community's health: a cross-sectional study on tobacco marketing in 1", Bulletin of the World Health Organizatio, Dec 2015 Issue Publication	<1%
234	"Abstracts", Journal of Thoracic Oncology, 2009 Publication	<1%
235	www.proefschriftenverpleegkunde.nl Internet Source	<1%
236	"Perioperative dexmedetomidine for acute pain after abdominal surgery in adults", Cochrane Database of Systematic Reviews, 2016. Publication	<1%

237	for the REsearching severe Sepsis and Organ dysfunction in children: a gLobal perspective (RESOLVE) study group. "Drotrecogin alfa (activated) in children with severe sepsis: a multicentre phase III randomised controlled trial", The Lancet, 20070310/16 Publication	<1%
238	van der Linden, N., M. Tieland, L.J.J. Klinkenberg, L.B. Verdijk, L.C.P.G.M. de Groot, L.J.C. van Loon, M.P. van Dieijen-Visser, and S.J.R. Meex. "The effect of a six-month resistance-type exercise training program on the course of high sensitive cardiac troponin T levels in (pre)frail elderly", International Journal of Cardiology, 2014. Publication	<1%
239	"13th European Congress of Clinical Microbiology and Infectious Diseases", Clinical Microbiology and Infection, 2003 Publication	<1%
240	Jen A. Tan. "Use of dexmedetomidine as a sedative and analgesic agent in critically ill adult patients: a meta-analysis", Intensive Care Medicine, 04/08/2010 Publication	<1%
241	"Geriatric Anesthesiology", Springer Nature, 2018	<1%

	Publication	
242	L. Tritapepe. "Cardiac protection by volatile anaesthetics: a multicentre randomized controlled study in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass", European Journal of Anaesthesiology, 04/2007 Publication	<1 %
243	Amer, Asmaa. "The effect of pre-emptive gabapentin on anaesthetic and analgesic requirements in patients undergoing rhinoplasty: A prospective randomised study. (Original Article)(Report)", Indian Journal of Anaesthesia Publication	<1 %
244	Tibazarwa, K.. "A time bomb of cardiovascular risk factors in South Africa: Results from the Heart of Soweto Study "Heart Awareness Days"", International Journal of Cardiology, 20090220 Publication	<1 %
245	B. J. Gersh. "Novel therapeutic concepts * The epidemic of cardiovascular disease in the developing world: global implications", European Heart Journal, 03/02/2010 Publication	<1 %
246	"You're Wrong, I'm Right", Springer Nature,	

	2017 Publication	<1%
247	"Annual Meeting of the European Society of Anaesthesiology Munich, Germany, June 9–12, 2007", European Journal of Anaesthesiology, 06/2007 Publication	<1%
248	Lucía Gallego-Ligorit, Marc Vives, Jorge Vallés-Torres, T. Alberto Sanjuán-Villarreal, Azucena Pajares, Mario Iglesias. "Use of Dexmedetomidine in Cardiothoracic and Vascular Anesthesia", Journal of Cardiothoracic and Vascular Anesthesia, 2018 Publication	<1%
249	Li, Bo, Yalan Li, Shushi Tian, Huixia Wang, Hui Wu, Aihua Zhang, and Chengjie Gao. "Anti-inflammatory Effects of Perioperative Dexmedetomidine Administered as an Adjunct to General Anesthesia: A Meta-analysis", Scientific Reports, 2015. Publication	<1%
250	Hausenloy, D. J., E. Boston-Griffiths, and D. M. Yellon. "Cardioprotection during cardiac surgery", Cardiovascular Research, 2012. Publication	<1%
251	Guarracino, F.. "Myocardial Damage Prevented by Volatile Anesthetics: A Multicenter	<1%

Randomized Controlled Study", Journal of Cardiothoracic and Vascular Anesthesia, 200608
Publication

252 Matthias Thielmann, Vikram Sharma, Nawwar Al-Attar, Heerajnarain Bulluck et al. "ESC Joint Working Groups on Cardiovascular Surgery and the Cellular Biology of the Heart Position Paper: Peri-operative myocardial injury and infarction in patients undergoing coronary artery bypass graft surgery", European Heart Journal, 2017 <1%
Publication

Exclude quotes	On	Exclude matches	Off
Exclude bibliography	On		